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THE INFLAMMATORY REACTION IN TUBERCULOSIS.*

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In approaching this subject on the occasion of the Gross Lecture, it is appropriate to recall the fact that Samuel Gross was the author of the first comprehensive treatise on pathologic anatomy published in this country,† which appeared in 1839, when Gross had just vacated the chair of General Anatomy, Physiology and Pathological Anatomy in the medical department of Cincinnati College.

It seems particularly apposite to our immediate purposes to recall the views of Gross himself on the two subjects of inflammation and tuberculosis. Thereby we may at the same time take pride in the accomplishments of the past century of endeavor in these fields, and be heartened, in the midst of our own serious perplexities, by the partial conquest of the confusion of thought frankly and forcefully depicted by Gross. Influenced by the current French teaching, which reached its extreme expression with Cruveilhier, Gross stated as a logical assumption that "as a general proposition, liable to few exceptions, all organic diseases, whatever be their seat or extent,

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† The earlier "Treatise on Pathological Anatomy," by William Edmonds Horner (Philadelphia, 1829), although treating certain phases of morbid anatomy in detail, did not attempt to cover in systematic fashion existing knowledge in all departments of this subject as did the "Elements of Pathological Anatomy" of Samuel Gross (Boston, 1839).

are the result of inflammatory action." But, he was careful to point out, "of the essence of disease very little, indeed nothing at all," was known. "The proximate cause of morbid action," he added with apparent resignation, "and the immediate cause of life in the healthy state, are as inscrutable to the human mind as the cause of gravitation, of attraction and repulsion. All we can boast of is that we know something of their effects; beyond this it is extremely problematical if we shall ever be able to penetrate. With this, indeed, every philosophical inquirer after truth should be contented, remembering that the secrets of Nature are not easily detected, and that to God alone belongs the knowledge of the intrinsic property of things." Yet this pious renunciation did not suppress the fundamental research instinct of this earnest investigator, for a scant 5 pages later he invites his reader to proceed with him "to investigate the nature of inflammation, its seat and the phenomena which characterize it."

With his comprehensive inclusions under the term "inflammation" it is not surprising that he considered the tubercle an inflammatory product; but this assumption did not lead him to omit proof in his specific discussion of tuberculosis. There was indeed in 1839 much opposed evidence. Drawing analogies from other types of inflammatory reaction, he reached the conclusion "that all tubercular matter, whatever may be its form, site and extent, is, in the first instance, of a liquid nature, and that it becomes solid only by the removal of the serosity which is always poured out simultaneously with it." In other words, he thought of tuberculous tissue as an exudative manifestation.

The problems that beset Gross in 1839 in understanding the nature of the tubercle were never solved, simply because all effort in this field took an entirely new direction a few years later with the development of the cellular pathology. It is perhaps not entirely gratuitous for me to suggest that the direction of our own efforts may also change in the not distant future with the establishment of unexpected new principles which may save us the necessity of ever solving certain of the troublesome and vexing problems to which I shall call attention tonight.

In a revised edition of his book in 1857, at the dawn of the cellular pathology, Gross supplemented his original exposition of the tubercle with a brief consideration of its cellular aspects. He did not yet see in the new knowledge confirmation of his original views on its inflammatory nature, but he had found no reason in the interim to change his opinion.

In Gross's time the definition of an inflammatory reaction was necessarily different from the several that are in vogue today, and in his view the current definitions were inadequate to cover the phenomena of tuberculosis. Particularly was the time-honored descriptive characterization, in terms of redness, heat, pain and

swelling, deficient. As he pointed out, in tuberculosis any or all of these might be lacking. Insisting on a local origin for every inflammation, he thought of the tubercle as a tissue deposit in reaction to some sort of irritant. Obviously the nature of the latter was entirely unsuspected. Doubtless Gross honestly considered it one of those intrinsic properties understandable only by God. The character of the lesion and its effects, rather than its cause, therefore received the greater part of his attention.

Since the time of Gross and his contemporaries there has been an increasing insistence on a beneficial attribute in the phenomenon of inflammation. Even before his time, certainly from the days of John Hunter, if not earlier, inflammation had come to be considered Nature's way, often ineffective and at the best expensive, of handling a body irritant. Most definitions today emphasize this protective aspect. It is doubtful if Gross, however, saw anything but the unfortunately inevitable in the course of tuberculosis, even though considering it an inflammation.

It was indeed a difficult task for later pathologists to uncover beneficial elements in the tubercle. To the early cellular pathologist the deposit of cells in the individual tubercle and the associated tissue destruction must have seemed as devoid of helpful aspects as the infiltration and destruction by a cancer. Even with the discovery of the tubercle bacillus, small consolation came to those seeking the protective element, for the disposition of the infecting agents within the cells, suggesting their multiplication there, seemed to indicate only a defensive mechanism for the parasite, and not for the unhappy host. It was only with the Metchnikovian era and the new concepts of phagocytosis that solid ground was found for advance with the view that exudative and proliferative aspects of tuberculosis were not only inflammatory in character, but also protective. And the most ardent optimist would have to admit that this protective mechanism was often not merely ineffective, but fraught with danger.

There is no doubt that most pathologists today think of the inflammatory reaction in tuberculosis in terms of its cellular aspects. The vascular changes and fluid exudation are looked upon as attendant phenomena and, by those most teleologically inclined, as attendant phenomena designed to bring to the site of the infection an army of fighting cells. And so much interest has developed in the characteristic cells entering into the structure of the tubercle, that discussions of the inflammatory reaction in tuberculosis have an inevitable tendency to resolve into inquiries on the source of the epithelioid cell.

Before succumbing to this trend, I should like to recall certain general principles of the inflammatory reaction in tuberculosis. In the first place—and this might be assumed, even if not known—the inflammatory response varies greatly, quantitatively and quali-

tatively, in different animal species. A special investigation of this variation in relation to resistance was made by Vorwald,[1] who studied the inflammatory response to human type tubercle bacillus infection in the guinea pig, rabbit, monkey, dog, cat, rat and chicken. His figures show no positive correlation between resistance and cellular reaction but, if anything, an inverse relationship. For example, when a comparison was made of the cellular response to tubercle bacilli in the guinea pig and cat, animals of respectively low and high resistance to tuberculous infection, the inflammatory reaction was found to be vastly greater in the former. The lesion characterized at the outset by the greater inflammatory response, proceeded and continued on a much less favorable course. Presumably those opposed to viewing inflammation as a protective mechanism might wish to use this observation in support of their argument. Certainly anyone looking upon the inflammatory response in the two species as protective would be forced to view the minimal response of the cat as much more effective qualitatively than the quantitatively superior response of the guinea pig. Without going into several other possibilities, I should like to say at once that many observers of this phenomenon would be inclined to dissociate resistance and inflammation in this case entirely, and would try to explain the difference in disease progress in the two animals by other and quite different factors favoring or discouraging survival of the infecting agent.

Before leaving this very interesting subject of variable reaction in animals may I call attention to the peculiar character of tuberculosis in the rat. The statement is often made that the rat is highly resistant to tuberculosis. The truth is that rats, at least most white rats, are not highly resistant, but the disease progresses with extreme slowness in their tissues. As a general rule, however, it progresses as relentlessly as a malignant tumor. This progress is in the face of, or some might say with the support of, a steady production of phagocytic cells that engulf the bacilli. Whether the outpouring of such cells is inflammation is perhaps an academic point only. At any rate within these cells the bacilli thrive until the continued multiplication of phagocytic cells surpasses the mechanical tolerance level of vital organs like the lungs, and the animal dies.

The next general principle meriting consideration is the variability of inflammatory response within an animal species. I refer especially to the modified inflammatory capacity conferred by previous tuberculous infection and the resultant so-called hypersensitiveness. Tuberculous infection does not always bring about the hypersensitive state. Certain animals, like the rat, seem to have no heightened inflammatory reactivity after a first infection. In man, cattle, pigs, fowls, guinea pigs and many other animals the capacity to respond to a new similar infection is greatly enhanced by a previous infec-

tion. This increased reactivity is most easily observed in the familiar Koch phenomenon in the skin. But experiment has shown that most other tissues share in the hypersensitive state, although not in equal degree. With this experimental control it seems fair to interpret certain intense reactions in man that occur in reinfections but not in first infections, as allergic phenomena. The list would include tuberculous pneumonia and the exudative responses of serous membranes. It is generally agreed, too, that in the more chronic phenomena of adult type pulmonary tuberculosis, including excavation (often rather superficially disposed of as a Koch phenomenon), hypersensitivity plays an important part.

The altered reactivity of the hypersensitive state seems to be expressed almost solely in increased speed and intensity of inflammatory response. Sometimes a special influx of certain cells, especially eosinophil leukocytes, is seen, giving a qualitative alteration to the picture, but in the main the difference in reaction from that of first infection lies in the wider dilatation of capillaries and much greater outpouring of plasma and wandering cells. We seem on sure ground in interpreting this enhanced reactivity seen in acute tuberculous inflammation in terms of hypersensitivity. It seems reasonable to suppose that the modified reactivity of chronic infection, however, is a more complicated matter. In recent years there has been an increasing tendency to dissociate the phenomena of allergy and immunity, a trend especially furthered by the extensive work of Rich,[2] and we may well believe that such matters as halted growth of bacilli, and their more rapid destruction, lead to a slow change in anatomic character of tuberculous lesions, even when lessened hypersensitiveness, or none at all, can be detected by the accepted tests for this phenomenon.

More intimately considered, hypersensitiveness involves a multitude of tissue structures. The most important seems to be the vascular endothelium. A small dose of tubercle bacilli in the skin, or in any of several other tissues, in a normal guinea pig causes a barely detectable local hyperemia. The same dose of bacilli in a previously infected and hypersensitive animal causes intense local vasodilation. The normal vasomotor capillary constriction is completely in abeyance, and blood pours into every capillary in the neighborhood. The extraordinary exudation that occurs when tubercle bacilli or certain elements of their substance come into contact with serous membranes, is also probably based in part on change in the vascular endothelium. When a small dose of tubercle bacilli is injected into the peritoneum of a normal guinea pig no appreciable immediate change can be noted. When the same dose is introduced into a tuberculous guinea pig (but one, I should add, with a normal appearing peritoneum), in a few hours the peritoneal coat is suffused with a delicate pink, is slightly swollen, and 10 to 15 cc. of plasma, containing a good many leukocytes, have oozed

into the peritoneal cavity. It is generally believed that the acute tuberculous effusions in man, such as pleuritis, meningitis, etc., are on a similar basis. Naturally in the more chronic manifestations of tuberculous serositis other factors, such as lymphatic blockage, play a part.

Of particular interest is the apparent sensitization of a wide variety of body cells. Among the most sensitive are the primitive germ cells of the testis. Small doses of tubercle bacilli and their products have no effect on these cells in the normal guinea pig. The same dosage causes prompt degeneration of these cells in the tuberculous animal, even through no known method permits us to see any previous difference in the cells concerned. Perhaps, however, I have digressed from the subject, in discussing a phenomenon not inflammatory but degenerative in nature. However, a similar, if not identical phenomenon can be discovered in leukocytes, which by common consent are intimately concerned with inflammation. Holst[3] and Stewart, Long and Bradley[4] have called attention to the toxic effect of tuberculin on leukocytes from tuberculous animals, contrasting it with the innocuousness of this substance for the same cells in normal animals. Rich and Lewis[5] and Aronson[6] have shown a similar effect of tuberculin in tissue culture on the wandering cells of the spleen and bone marrow of tuberculous guinea pigs. These results were obtained with tuberculin and not tubercle bacilli, but, as I shall point out later, it is "tuberculin" that is largely responsible for the acute response in tuberculous infection. Apparently the effect of tubercle bacilli and their specific product tuberculin on leukocytes is in accordance with the general pharmacologic law that small doses of injurious substances stimulate, whereas large doses kill. The enormous output of polymorphonuclear leukocytes in tubercle bacillus reinfection and in the tuberculin reaction is a familiar picture, and if the capillaries are examined under these conditions it will be found that they are crowded with leukocytes. Apparently in the tuberculous and hypersensitive animal, tubercle bacilli have a far greater chemotactic effect than in the normal animal, and the total inflammatory response is correspondingly altered. An increased phagocytic action by the leukocytes of the infected animal has long been known (Meakins[7]), and has been shown to be associated with the presence of serum antibodies (McCutcheon, Strumia, Mudd, Mudd and Lucké).[8]

At this point it is perhaps appropriate to attempt an analysis of the inflammatory reaction in tuberculosis in terms of the elements of the bacillus that appear responsible for different phases of the tissue response. It is now well known that most of the anatomic features of experimental tuberculosis can be reproduced by the injection of certain purified substances obtained from the bacillus. The tuberculin reaction is an illustration in point. The acute inflammatory response elicited when tubercle bacilli are introduced into

the tissues of a tuberculous animal seems no different from the reaction obtained if an extract of the bacillus, certain nitrogenous products of its growth or, finally, a pure protein isolated either from the bacillus or the medium of its growth, be substituted for the living microörganism. Minute amounts of this protein, which has been studied exhaustively by Seibert,[9] call forth an acute reaction in tuberculous guinea pigs, which is grossly and microscopically indistinguishable from that produced by an equivalent amount of tubercle bacilli. Certain derivatives of this protein, which probably occur in quantity in ordinary tuberculin, incite a closely similar response.

A close likeness of the tubercle itself, and of chronic proliferative tuberculosis, can be brought about through the use of another class of substances that can be isolated from tubercle bacilli. A group of highly purified lipoids have been prepared from these microorganisms by Anderson,[10] which have been found by Sabin[11] and her coworkers to produce masses of new tissue much like tubercles. Of the several lipoids isolated and purified, a phosphatid has proved the most active in stimulating the formation of tuberculous tissue, and its effect on the production and changing appearance of epithelioid cells is such as to lead Sabin to consider tuberculosis in some respects a "phosphatid disease."

Having discussed some of the more general phases of cellular reaction in tuberculous infection, we may now consider the nature of the cellular response itself. It has been known for many years that the immediate reaction when tubercle bacilli are introduced within the tissues is an outpouring of polymorphonuclear leukocytes, and everyone familiar with the histology of the reaction of reinfection is aware that this cellular exudation is greatly intensified by hypersensitiveness. Relatively little stress has been laid upon this polymorphonuclear response, but it is really of more than passing significance. Vorwald[12] has made a careful study of the early reaction to intravenous injection in the rabbit lung, which emphasizes the localizing effect of the response upon the bacilli introduced. In less than an hour after the injection all the bacilli are within polymorphonuclears, and the latter are aggregated into tight masses which represent the site of subsequent tubercle development. Within a few hours phagocytosis of the bacillus-laden polymorphonuclears by large mononuclears occurs, and is followed by their digestion, so that at 24 hours only traces of the former may remain, with the bacilli lying free in the cytoplasm of the large mononuclears. Thus the determinative effect of the polymorphonuclear response upon the localization of the tubercle is clear. It may be suspected that the polymorphonuclear leukocyte that holds the bacillus for a time may have some effect on the microörganisms, supplementing the later action of the large mononuclear, but nothing definite in this respect is known.

On reinfection, the same phenomenon of initial polymorphonuclear response with prompt localization of the bacilli is observed. The only difference is that the cellular outpouring is faster and on a greater scale. Whether or not destruction of the bacilli is aided in this process, the inflammatory reaction must constitute a significant impediment to spread of the bacilli by way of the body fluids. Krause[13] and Willis[14] have laid great stress on the localizing effect of the allergic reaction on tubercle bacilli injected into the skin of tuberculous animals and, as I have taken pains to show, the first localization is carried out almost exclusively by the polymorphonuclear cells.

Although relatively little attention has been paid to the polymorphonuclear reaction that I have just discussed, there has been enormous concentration of effort on the source, nature and activity of the large mononuclear cells which, in various stages of transformation, make up the more mature tubercle. The same cells are of course concerned in chronic inflammations in general and, as Opie[15] has recently stated concisely, "The problem of the origin of these cells is nearly half a century old, and whether they come from the blood stream or from the fixed tissues or both is no better understood when their accumulation accompanies the healing of a pyogenic abscess than when as 'epithelioid cells' they form the essential element of the tubercle."

Among the many complicating factors in determining the origin and rôle of the large mononuclear phagocytes in tuberculosis, are the variations in their form and action in different animals used for experimentation and even in different organs of the same animal. Corper and his associates[16] have noted a great variability in the accumulation of particulate matter, including tubercle bacilli, in the fixed phagocytes of different organs, and Lurie[17] has presented evidence of a greater destructive capacity for tubercle bacilli in the mononuclear cells of the liver, splenic pulp and bone marrow than in those of lung, kidney and spleen corpuscle. Among the first significant studies on the source of the epithelioid cell was that of Evans, Bowman and Winternitz,[18] who found by the simultaneous injection of vital dyes and tubercle bacilli that in the liver it was the Kupffer cells from which growing tubercles originated. But even in this case it appeared evident to the authors that in the course of development of epithelioid cells from Kupffer cells, numerous large mononuclears of different source were enmeshed in the growing mass and henceforth took part in the tubercle formation.

In the lung a predominant rôle has been credited to the alveolar phagocyte, but the origin of this cell has long been in continued dispute. At present there seems to be a tendency to agree that it is a mesenchymal fixed tissue cell of the alveolar septa (Gardner and Smith,[19] Fried,[20] Lang[21] and others), but there is evidence that

a good many of the mononuclears in lung tubercles and other pulmonary inflammations come from the blood stream also (Foot[22]).

In the peritoneal cavity the situation is at least as complicated. Sabin[11] and her coworkers have laid great stress on depots of primitive monocytes in the so-called "milk spots" of the omentum. On injection of tubercle bacilli or tubercle bacillus lipoids into the peritoneal cavity multiplication of these cells occurs, according to their reports, with the production of tubercles. At first a rather sharp distinction was drawn between the long known, large fixed-tissue phagocytes, or clasmatocytes, and the monocytes, which could be found in a similar form both in tissues and the blood. Gardner,[23] however, in examining the peritoneal reaction to primary and superinfection in the rabbit, was unable to discover any difference other than in physiologic activity between these two cells in the peritoneal exudate. What he did find were masses of cells of this general class adhering to the free surfaces of the cavity a few hours after infection. They appeared to arise from cells of the same sort, of undetermined prior origin, and to give rise to large masses of mononuclear cells through mitotic division.

I have cited but a minute fraction of the literature on this detail of tubercle formation, the origin of the epithelioid cell, but I may simply say, as to the rest, that the mass of evidence presented is almost hopelessly confusing. Many skilled cytologists, not primarily pathologists, have entered into the problem without settling it. It therefore must appear presumptuous for one with no such skill to take part in such a competition. Yet I should like, very briefly, to present some evidence of my own on the subject. I may say in advance that it also is inconclusive. It seemed to some of my associates and myself that the cornea, a nonvascular, extremely simple structure, might be a good place to study the details of tubercle formation. To be sure this was the very first tissue in which a serious study of the problem had been made, but much useful information, enabling better interpretation of results, has accumulated since Baumgarten studied corneal tuberculosis in the same quest 50 years ago. My associate, Holley, and I[24] found that no significant proportion of large mononuclear cells appeared at the site of tuberculous infection of the cornea until vessels approached the spot. When the infection was at the limbus vascularization and mononuclear infiltration occurred early; when the lesion was at the center both were much delayed. It seemed unquestionable that the influx of mononuclears, replacing the early invading polymorphonuclears, was a consequence of the new bloodvessels. Examination of the latter seemed to furnish a clue. Almost everyone of them was surrounded by a collar of mononuclear cells, which could be traced in successive stages out to developing epithelioid cells. Much difficulty still remained in determining their original source. They occurred not only around the new capillaries but also in their

walls. Had mitoses been numerous we could easily have concluded that they were fixed-tissue cells of the vascular walls multiplying as do other fixed cells. But very frequently cells of identical sort could be seen in the vessel lumina, and occasionally such cells could be seen migrating into and through the vessel walls. This was evidence that the blood monocyte was the source of the perivascular collar of cells, which in turn gave rise to the cells of the growing tuberculous tissue. Colleagues who examined the sections reminded us of the possibility that the migration was the other way, that the cells in the vessel lumina might be coming in and not going out. I shall not dwell upon this experiment longer, because the need for a different type of study, permitting observation of the transit of living cells, is obvious, but my impression remained that a considerable portion of the mononuclear cells partaking in the reaction passed into the vessel walls from the blood stream, slowly accumulated there, gradually migrated into the perivascular tissue, and subsequently underwent increase in size and change in form and became the large mononuclear and epithelioid cells of the tubercle. The process appeared to be accompanied by a minimum of mitosis; this was perhaps the chief argument against a fixed-tissue origin. In fairness I must admit that amitotic division of adventitial cells could have given rise to the same picture.

This fragmentary account of the inflammatory reaction in tuberculosis should be supplemented with some consideration of the effect of the cells concerned on the viability of the infecting microorganism. As I have said, many pathologists are accustomed to add to their definition of inflammation some teleologic reference to the effect on the injurious agent. As I mentioned a few moments ago, the rôle of the polymorphonuclear leukocyte, other than in its mechanical capacity, has not been determined. As for the mononuclear phagocyte, it is a curious fact that it has been both insisted and denied categorically that this cell destroys the tubercle bacillus within its cytoplasm. The truth seems to be that under some conditions it is effective in this respect, and in others not. To this statement it might be added that the mononuclears of some animal species exert a destructive action, whereas those of others permit growth. Important evidence on this subject has been secured through the investigations of Lurie,[17] who has traced the rise and fall of the bacillary population of the organs of infected rabbits and guinea pigs by counting the colonies of tubercle bacilli that may be isolated from unit weights of these tissues. Multiplication of bacilli, according to his experience, was accompanied by rapid mitotic multiplication of large mononuclear cells. Subsequent decreases in the bacillary count of any tissue were regularly found associated with transformation of the mononuclears into epithelioid cells. It seemed a sound conclusion that the epithelioid cell was a

large mononuclear that had destroyed and partially digested tubercle bacilli.

This view is in contrast with the earlier conclusion of Sabin that the monocyte and its descendant, the epithelioid cells, do not destroy tubercle bacilli, but rather act as nutrient hosts for them, a conception that appears warranted under some conditions of infection. On the other hand Lurie's view is quite in harmony with Smithburn and Sabin's[25] more recent picturization of the epithelioid cell as a cell that has reached its distinctive cytoplasmic state through emulsification of phagocytized tubercle bacillus phosphatid. As they have described it, "The lipoid is phagocytized by monocytes, or, if the stimulus be great enough, by the primitive cells which give rise to monocytes. After the lipoid has been phagocytized it is subjected to a process of intracellular dispersion into finer and finer droplets. After reaching the stage of the finest droplets, no further detectable change takes place."

In all this discussion I have purposely omitted reference to the lymphocyte in the tubercle. It has seemed to me that a large part of the literature on this subject is of uncertain value through failure to identify the cell concerned. What many have been content to label a simple lymphocyte is considered a primitive monocyte by some, whereas others insist that the monocyte is itself a derivative of a primitive lymphocyte. A direct relation between lymphocytosis and resistance to tuberculosis is generally conceded, but the exact relationship of the lymphocyte to the other cells of the tubercle is so much in dispute as to make present discussion of this point unprofitable.

I have floundered in a difficult subject, but in conclusion I would refer again to the perplexities of Samuel Gross in the field I have been discussing. When the first edition of his "Elements of Pathology" was published in 1839, the difficulties he encountered in defending his view of the tubercle as an inflammatory product and understanding its character were formidable and far from solution. In 1857, in the third edition of this book, he repeated most of what he had written in 1839, but added a drawing, with a few paragraphs, showing cells entering into the structure of the tubercle. He attached them as a supplement to his earlier exposition rather than as a solution of his problems. These, however, were never solved, for in the following year, 1858, appeared Rudolf Virchow's "Cellular Pathology Based on Physiological and Pathological Histology," and the worries of Gross and his contemporaries about a deposit of mysterious coagulable fluid in tissues, and subsequent transformation through a clotting nodule to a cheesy mass, were rapidly forgotten. Similarly the vexing cellular problems that I have indicated tonight may be resolved through the discovery of new principles in the large field of physiology, when the details that trouble us may appear inconsequential.

In the meantime the search for facts that will bring into harmony the various views on the origin of the most characteristic cells of the tubercle is being vigorously pressed, as is the effort to bring about a clear understanding of their function and their relation to growth or destruction of the infecting microörganism. The recent extensive work on the action of various chemical fractions of the tubercle bacillus has thrown much new light on these problems, and the introduction of new methods of studying living cells, supplementary to the use of fixed tissue preparations, has also been highly fruitful. Further progress may be expected in both lines. In any event, however, it is obvious that the inflammatory reaction is only one side of the balance in tuberculosis. The physiologic mechanisms concerned in the growth of the etiologic agent are quite as significant for the course of the disease as the inflammatory mechanism, which appears designed by nature to suppress the infecting element. The one field should be cultivated quite as extensively as the other.

Summary. The acute inflammatory response to tuberculous infection varies greatly in different animal species. Its intensity does not correspond directly with the resistance of the species to the disease. In certain animals of low resistance an intense initial cellular response occurs, and in others with high resistance the initial response is slight. In other comparisons no correlation at all can be observed. Factors other than success or failure of inflammatory suppression play a part in determining the fate of the infecting agent.

Within an animal species the intensity of response to tubercle bacilli may vary widely, the chief modifying factor being the hypersensitiveness conferred by previous infection with this microorganism. Not all susceptible animals develop hypersensitiveness. In the hypersensitive animal the inflammatory reaction to tubercle bacilli develops with greater speed and is of greater intensity. Otherwise the reaction is similar to that of first infection. Many cells are affected in the hypersensitive state, including the vascular endothelium and the various types of leukocytes.

The inflammatory reactions of tuberculosis can be reproduced by the use of pure substances extracted from the body of the tubercle bacillus. Chronic productive inflammation is caused by certain tubercle bacillus lipoids, and acute exudative inflammation, similar to acute tuberculosis in man, is caused in the hypersensitive animal by a tubercle bacillus protein and some of its derivatives.

The first cells responding to injection of tubercle bacilli are the polymorphonuclear leukocytes. They rapidly engulf and localize the bacilli, thereby determining the site of tubercle formation. Within 24 hours the polymorphonuclears are phagocytized and destroyed by large mononuclear cells, which complete the development of the tubercle.

The source of these mononuclear cells is still in dispute. It

appears to vary in different organs. In the liver and lung a high percentage of the mononuclear cells of developing tubercles arise from previous fixed tissue phagocytic cells (Kupffer cells and "alveolar phagocytes"). In the omentum, primitive cells apparently identical with blood monocytes give rise to epithelioid cells. In all of these locations, however, blood mononuclears take some part in tubercle formation.

The part played by the mononuclears of the blood is well shown in the cornea. When this normally avascular organ is infected with tubercle bacilli (rabbit, guinea pig, cat) the site of infection, although rapidly permeated by polymorphonuclears, is not invaded by mononuclears until new bloodvessels approach. The new capillaries are seen to be surrounded by collars of large mononuclear leukocytes. Among these mitotic figures are very rare. Migration figures from the vascular lumina are faily common, and large mononuclears, in considerable excess over the quantity normally found in the blood, can be seen in small vessels. The mononuclears, which thus appear to come largely from the blood stream, wander away from the vessel walls and by hypertrophy and change in structure, without division, become epithelioid cells.

The distinctive cytoplasmic state of the epithelioid cell appears to be the result of destruction of many tubercle bacilli and progressive emulsification of their lipoid.

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DIAGNOSIS OF EARLY TUBERCULOSIS.

THE VALUE OF MONOCYTIC LYMPHOCYTIC INDEX DETERMINED BY SUPRAVITAL TECHNIQUE BEFORE AND AFTER THE ADMINISTRATION OF TUBERCULIN.

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IT is often difficult to make a certain diagnosis of early pulmonary tuberculosis and clearly to differentiate it from numerous other diseases. Usually the physical examination and laboratory data do not offer much on which to base a diagnosis. It is exceptional that bacilli are found in the sputum in the early stage. A blood count may or may not show a slight anemia with a leukopenia or a normal white cell count or a leukocytosis, and on a fixed smear the differential may show an increase of large mononuclear cells or polymorphonuclear cells or lymphocytes. Any one such blood picture of itself is no great help. Frequently a chest plate shows peribronchial infiltration or increased hilar markings or thickened pleura or a combination of these "indicative but not diagnostic lung signs." It is at this point that there is need of confirmatory diagnostic aids.

In the past few years the diagnostic (and prognostic) importance in tuberculosis of the monocyte-lymphocyte index and the total monocytes determined by supravital technique of Sabin have been stressed by numerous investigators. In 1925 Cunningham, Sabin, Sugiyama and Kindwall,[1] using the supravital technique of Sabin,[2] studied the white blood cells in 75 rabbits after the majority had been inoculated with bovine tuberculosis cultures and a few with human tuberculosis cultures. They concluded that the effect of the tubercle bacillus on the whole system was a profound one, that it consisted in a marked overproduction of diffusely scattered reticular cells, which are the parent cells of monocytes, as well as the other white cells. The particular effect of the tubercle bacillus on the reticular cell was definitely to force it toward the production of monocytes. They determined that the ratio of monocytes to lymphocytes was of fundamental importance. They found that normally the average ratio was: monocytes, 943; lymphocytes, 2805; index, 2.9. When the reaction to disease was very unfavor-

able the ratio was: monocytes, 3469; lymphocytes, 2799; index, 0.8. When the reaction to disease was favorable the ratio was: monocytes, 854; lymphocytes, 3047; index, 3.6. Thus a marked and continued reversal of the normal ratio, provided the monocytes were increased in actual number, was a consistent indication of the malignant stage in the reaction of the animal to the disease. The reverse was likewise true when the lymphocytes were markedly and consistently higher than the monocytes, even though the actual number of monocytes was somewhat above normal, they found arrested tuberculosis without fail.

In 1928 Cunningham and Tompkins[3] studied with the same technique the white blood cells of 71 tuberculous patients. For a normal standard of human blood as a comparison they used the figures of Sabin, Cunningham, Doan and Kindwall.[4] They likewise concluded that the monocytes in the blood are practically always increased in tuberculosis (and are stimulated in phagocytic activity), that the changes parallel the grade of clinical activity, that lymphocytes in the blood are an index of resistance and parallel increased resistance, and that the relation of monocytes to lymphocytes is a useful mathematical expression for the extent of invasion compared to that of resistance.

In 1929 Blackfan and Diamond,[5] studying the bloods of 17 infants with the Sabin technique, demonstrated the same principle of monocyte-lymphocyte relationship, and in 1931 Hamil[6] arrived at similar conclusions after an evaluation in infants and children of monocyte counts by the supravital staining method.

In 1931 Grieger,[7] working under the direction of Cunningham, performed experiments which indicated that there was no storehouse for monocytes in normal nontuberculous animals capable of supplying large numbers of these cells on acute demand, but that such a storehouse was developed in the tuberculous animal. He injected suspension of colon bacilli into tuberculous and nontuberculous animals. In the nontuberculous animals after injection he obtained a moderate leukocytosis with a marked increase of the neutrophils, a decrease of the lymphocytes and a slight decrease of the monocytes. In the tuberculous animals after injection there was a marked leukocytosis with a marked increase in the monocytes, a moderate increase in the neutrophils and a slight decrease in the lymphocytes.

A practical application of these studies seems apparent, as they might be valuable in the diagnosis of early tuberculosis. Since monocytes are increased in tuberculosis and the monocytic-lymphocytic index is of such importance diagnostically, monocytes should be increased dramatically in tuberculous subjects after focal tuberculin is administered, and monocytes should not be increased after administration to normal nontuberculous patients, as there is no storehouse in the normal which is capable of supplying large numbers of these cells on acute demand (systemic reaction to tuberculin).

TABLE 1.—TABULATED CASE DATA.

Date.	Total W. B. C.	Mono.	Lym.	Index.	O. T.	
4/17	....	....	....	....	.....	Case 1, male, aged 24 years; hemoptysis in 1930; in tuberculosis ward for 3 mos.; Roentgen ray: peribronchial and vesicular infiltration in upper lobe of right lung and thickening of lower bronchial trees; in midlung zone on right side is evidence of small cavity.
4/21	7,000	140	840	6.0	½ mg. I. D. 1½ mg. S. C.	
4/22	13,000	910	1,040	1.0	.....	Slight local but no focal reaction.
4/23	11,000	440	2,860	6.5	.....	Reaction entirely cleared up; no fever; Roentgen ray: no evidence of focal reaction.
8/14	....	....	....	....	.....	Case 2, male, aged 45 years; chronic cough, loss of 25 pounds; râles in left apex; Roentgen ray: peribronchial and vesicular involvement of both lungs, more extensive on left.
8/18	8,000	240	1,120	4.6	½ mg. I. D. 1 mg. S. C.	
8/20	9,500	760	1,040	1.3	.....	Local reaction; increase in fever; aggravation of physical signs; Roentgen ray: tracheobronchial adenopathy and thickening of bronchial trees on both sides, more marked on left; there is evidence of vesicular involvement and numerous small cavities in midlung zone on left.
8/21	7,000	560	840	1.5		
2/11	....	....	....	....	.....	Case 3, male, aged 30 years; hemoptysis, dyspnea, fever, loss of weight; apparent emaciation; harsh breath sounds; no râles; Roentgen ray: hilar shadows exaggerated; the apical pleura is thickened; considerable peribronchial infiltration in hilar zone of first interspace with slight vesicular involvement of right apex and infraclavicular region on the left side.
2/23	8,500	510	1,360	2.4	½ mg. I. D. ½ mg. S. C.	
2/24	9,000	450	1,530	3.4		
2/26	9,000	540	1,620	3.0	.....	No reaction.
2/27	....	....	....	....	2½ mg. S. C.	
2/28	11,000	2,200	1,100	0.5	.....	Definite local and focal reaction; rise in fever, continued reaction (râles heard, right apex).
3/1	10,000	2,000	1,000	0.5	.....	Roentgen ray: focal reaction in hilar zone of first and second interspace and in right apex.
3/5	11,000	2,640	1,320	0.5		
3/6	10,000	1,600	800	0.5		
8/3	....	....	....	....	.....	Case 4, male, aged 31 years; loss of weight; chronic cough, chest pains; undernourished; physical signs of thickened pleura; Roentgen ray: evidence of adhesions between visceral and diaphragmatic pleura at costophrenic angle on both sides; thickening of interlobar pleura on right side, thickening of apical pleura on both sides; no definite vesicular involvement.
8/15	6,000	60	1,440	26.0	½ mg. I. D. ½ mg. S. C.	
8/16	5,500	550	990	1.8	.....	Marked local and febrile reaction.
8/17	6,000	600	720	1.2	.....	Roentgen ray: evidence suggestive of slight focal reaction in hilar and midlung zone of first interspace on right side.
8/14	....	....	....	....	.....	Case 5, male, aged 26 years; cough, loss of weight, weakness; no definite physical signs; Roentgen ray: considerable increase in lung markings with thickening of lower bronchial tree on right side; no definite vesicular involvement.
8/25	7,000	560	980	1.7	½ mg. I. D. 1 mg. S. C.	
8/26	9,000	1,080	1,260	1.1	.....	Marked local reaction; marked febrile reaction.
8/27	12,000	2,160	960	1.5		
8/28	20,000	3,200	1,600	0.5	.....	Roentgen ray: focal reaction in hilar zone of second interspace.
8/10	....	....	....	....	.....	Case 6, male, aged 30 years; weight, 120 pounds; pain in chest (substernal) aggravated by working; loss of weight; cough; bronchial breathing right apex; Roentgen ray: hilar shadows exaggerated and peribronchial infiltration in perihilar zone; no definite vesicular involvement.
9/1	9,000	450	2,250	5.0	½ mg. I. D. ¼ mg. S. C.	
9/2	8,500	850	785	0.92	.....	Slight local reaction, febrile reaction.
9/3	11,000	1,100	1,320	1.2	.....	Roentgen ray: no evidence of tuberculin reaction; patient refused treatment, returned to work.
9/15	....	....	....	....	.....	Rectal abscess developed; he lost 15 pounds.
11/14	....	....	....	....	.....	Roentgen ray: evidence of slight vesicular involvement in right apex which was not seen in previous examination.
9/15	....	....	....	....	.....	Case 7, male, aged 17 years; loss of weight; no definite physical signs; Roentgen ray: exaggerated hilar shadows; no evidence of vesicular involvement.
10/1	8,000	320	960	3.0	½ mg. I. D. 1½ mg. S. C.	
10/2	....	....	....	....		
10/3	9,000	900	990	1.1	.....	No local reaction.
10/4	9,000	900	900	1.0	.....	Roentgen ray: evidence suggestive of slight reaction of lungs in hilar zone of right lung opposite second interspace.
3/27	....	....	....	....	.....	Case 8, male, aged 28 years; loss of weight, hemoptysis, negative sputum; exaggeration of breath sounds bilateral; Roentgen ray: peribronchial infiltration of apical and first interspace on left side; hilar shadows exaggerated; lower bronchial trees thickened; no vesicular involvement.
4/8	4,000	200	920	4.6	½ mg. I. D. ½ mg. S. C.	
4/9	5,000	250	1,250	5.0	..... 3 mg. S. C.	No febrile, no local reaction.
4/10	5,000	250	1,000	4.0	.....	Marked local reaction; febrile reaction; Roentgen ray: evidence pointing to slight focal reaction in hilar zone of the first interspace on right side of right apex.

TABLE 1.—TABULATED CASE DATA —(*Continued.*)

Date.	Total W. B. C.	Mono.	Lym.	Index.	O. T.	
3/20	8,000	720	2,320	3.2	½ mg. I. D.	Case 9, female, aged 14 years; anorexia, fever, nervousness;
3/21	85,000	850	2,250	2.6		P.E. negative; Roentgen ray: hilar shadows markedly exaggerated and considerable peribronchial infiltration especially
3/25	....	....	....	....	2½ mg. S. C.	on right side and at base of both lungs; the interlobar pleura between upper and middle lobes is thickened; no definite vesicular involvement.
3/26	9,000	360	2,340	6.0	.....	No focal, no local reaction.
3/27	9,500	380	1,900	5.0	.....	Roentgen ray: no focal reaction.
8/20	10,500	420	1,260	3.0	.....	Case 10, male, aged 28 years; headaches, loss of weight; in-
8/25	10,000	800	1,200	1.5		creased expiratory phase over right apex; Roentgen ray:
8/26	....	....	....	....	1 mg. I. D.	exaggerated hilar shadows; evidence of thickened pleura
					1 mg. S. C.	(left apex); lung markings increased; no evidence of vesicular involvement.
8/27	10,000	700	1,200	1.7	.....	Marked local reaction; marked febrile reaction; Roentgen ray: no evidence of focal reaction.
9/19	....	....	....	....	.....	Case 11, male, aged 30 years; influensa in 1918; chronic cough;
11/1	7,000	350	1,050	3.3		Roentgen ray: peribronchial infiltration of apical and first
11/2	....	....	....	....	½ mg. I. D.	interspace bronchi on left side; the midlung zone of the sec-
					1½ mg. S. C.	ond interspace on right side shows an area of lung reaction
11/3	6,000	360	960	2.9		which is suggestive of vesicular involvement.
11/4	8,000	400	1,200	3.0	.....	Slight local reaction; no febrile reaction; Roentgen-ray: no evidence of lung reaction from tuberculin.
8/27	....	....	....	....	.....	Case 12, male, aged 15 years; pains in chest; no loss of weight;
9/2	8,000	320	1,440	4.6	½ mg. I. D.	Roentgen ray: peribronchial infiltration of apical and first
					½ mg. S. C.	interspace bronchi on left side; evidence pointing to slight vesicular involvement in left apex.
9/3	9,000	360	1,640	4.5	.....	Slight reaction locally.
9/4	9,000	540	1,080	2.0	.....	Roentgen ray: no focal reaction; lung fields clear.
4/6	....	....	....	....	.....	Case 13, female, aged 12 years; weakness, inability to gain
4/8	5,000	200	1,750	9.7		weight; Roentgen ray: tracheobronchial adenopathy and
4/13	5,500	220	605	2.7		considerable peribronchial infiltration in perihilar zone on
4/14	6,500	390	1,560	4.0	1 mg. I. D.	right side.
					2 mg. S. C.	Fever, 102° to 103° F., which developed within 8 to 10 hours.
4/21	6,000	180	1,620	9.0	.....	A very severe local reaction; entire forearm became swollen; neutrophils increased from 61 to 90 per cent.
4/22	10,000	100	800	8.0	.....	Roentgen ray: EPA view of chest shows no evidence of focal reaction.
8/14	9,000	360	1,080	3.0	½ mg. I. D.	Case 14, male, aged 22 years; pain in right side of chest; cough;
					1 mg. S. C.	pain aggravated by coughing; Roentgen ray: EPA view of
8/15	7,500	450	1,050	2.3		chest shows median lobe abscess.
8/16	5,500	220	770	3.5	.....	No reaction, either local or focal.
7/17	....	....	....	....	.....	Case 15, male, aged 13 years; undernourished, pale; indefinite
9/10	9,000	450	1,080	2.4	½ mg. I. D.	physical signs; Roentgen ray: tracheobronchial adenopathy
					½ mg. S. C.	with peribronchial infiltration and reaction in first interspace left side; no evidence of vesicular involvement.
9/11	8,500	425	1,010	2.3	.....	No local reaction, no febrile reaction.
9/12	9,000	450	1,170	2.6	.....	Roentgen ray: no evidence of focal reaction.

NOTE.—Total W. B. C. = total white blood cells; Mono. = monocytes; Lym. = lymphocytes; O. T. = old tuberculin; I. D. = intradermally; S. C. = subcutaneously.

Wells and Long,[8] who have reviewed the complex and controversial subject of tuberculin, state that the majority of investigators today consider the tuberculin reaction a specific one for tuberculous animals sensitized by dead tubercle or related bacilli. Practically all observers agree that the substance responsible for tuberculin potency is a protein or a protein disintegration product. True, there are albuminoses and proteins in the filtrate which are not specific and which sometimes produce reactions similar to true general tuberculin reactions, but, as a rule, such febrile reactions resulting from nonspecific foreign protein usually occur within 8 or 10 hours, whereas the true specific tuberculin reaction is accompanied

by fever and a rise in basal metabolism 24 hours after the injection (Frisch[9]).

Roentgenologic changes in the lung are not likely to occur after a false tuberculin reaction, unless the reaction is a violent one, and a latent process is made active because of damage to the entire organism and resulting lowered resistance therefrom. The lung changes, however, would not be evident for some time, whereas there are demonstrable roentgenologic signs at the height of a true focal tuberculin reaction, that is, 24 to 48 hours after tuberculin is administered.

In order to demonstrate the above principles 15 patients were selected from the Charity Hospital Out-patient Clinic. Two of these patients were known to be tuberculous. The other 13 were young adults in whom it would have been almost impossible to confirm or deny a provisional diagnosis of early pulmonary tuberculosis. All were given old tuberculin intradermally and subcutaneously, in dosage ranging from 0.5 to 1 mg. intradermally, and 0.75 to 3 mg. subcutaneously, and the monocyte-lymphocyte index studied before and after at the height of the focal reaction or at the time the reaction was likely to occur.

Patients 1 and 2 were those known to have had tuberculosis. The first patient, aged 45 years, had been ill for over 10 years. After administration of 0.5 mg. old tuberculin intradermally, and 1 mg. old tuberculin subcutaneously, there was a marked increase of the monocytes from 240 to 760 and shift of the index from 4.6 to 1.3. Simultaneously there was an aggravation of the physical signs in the lungs, a rise in fever and a marked local reaction. The other patient had definite evidence of pulmonary tuberculosis for 5 years. After the administration of 0.5 mg. old tuberculin intradermally, 1.5 mg. old tuberculin subcutaneously, there was a marked increase in the monocytes from 140 to 910 and a shift of the index from 6 to 1. Simultaneously there was a slight local, but no focal, reaction to the tuberculin. There was no rise in fever. Previously (1929 to 1930) this patient had failed to react to focal tuberculin, although he was definitely tuberculous.

In 5 cases (Cases 3, 4, 5, 6, 7) a marked increase in monocytes was obtained simultaneously with the provocation of a focal reaction in the lungs. In only 1 (Case 7) of this group was there any doubt that there was a true focal reaction in the lungs. However, subsequent Roentgen studies, together with physical signs, marked loss of weight and the development of a fistula *in ano*, marked him as truly tuberculous. The monocyte response with monocyte-lymphocyte shift proved to be of more diagnostic value than the Roentgen examination, which failed to demonstrate a focal reaction. The focal reaction accompanied by a monocyte increase and an index shift we regarded as a very strong indication of the presence of tuberculosis.

In Case 8 there was no monocyte response after tuberculin and there was a questionable focal reaction in the lungs.

The patients in 7 cases were regarded as nontuberculous. In none of them was there a focal reaction or an appreciable increase in monocytes. Cases 9, 10, 11, 12, 13, 14 and 15 did not develop fever. One patient (Case 13) developed a marked local reaction, leukocytosis with an increase of the neutrophils from 61 to 90 per cent and an actual decrease in the number of monocytes. There was no evidence of definite focal reaction in the lungs and the fever occurred within 8 or 10 hours after injection, so the local swelling of the arm was considered as nonspecific and due probably to a reaction from protein to which she was sensitized.

The degree of monocyte response is not proportional to the amount of tuberculin administered. The following table, in which are listed the 7 positive cases, clearly illustrates this.

Type of pulmonary tuberculosis.	No. of case.	Old tuberculin administered mg.).	No. of times monocytes were increased.
Minimal B	3	2½	6.0
Moderately advanced (quiescent)	1	2	6.0
Minimal A	7	2	3.0
Chronic moderately advanced B	2	1½	3.5
Minimal A	5	1½	3.4
Minimal B	6	1¼	5.4
Minimal A or B	4	1	21.6

Cases 5 and 3 were about equal in the grade of clinical severity. In Case 5 the total number of monocytes was increased 21.6 times following the administration of 1 mg. of tuberculin, whereas in Case 3 the total number of monocytes was increased only 6 times following the administration of 2.5 mg. of tuberculin. Other similar cases (Cases 8, 6, 7) likewise showed no proportional relationship. The patients with moderately advanced pulmonary tuberculosis (Cases 1, 2) were given 2 mg. and 1.5 mg. of tuberculin, respectively. The increase in monocytes was 6 times in the former, 3.5 times in the latter. It seems, therefore, that although significant monocyte increase with shifting monocyte-lymphocyte indices coincides with specific focal tuberculin reactions, it would be fallacious to reason further that the greater the degree of monocytosis the more marked the grade of tuberculosis. Suffice it to say, that when there is a marked calling forth of monocytes from their "storehouses" after the administration of tuberculin, the diagnosis of tuberculosis is very likely.

Subsequent examinations of these patients many months later confirmed our first impressions.

Summary and Conclusion. It has been demonstrated that the monocyte plays an important rôle in tuberculosis. An increase in the number of monocytes of the circulating blood is indicative of

activity. A study by the Sabin technique of the number of monocytes and relative proportion of monocytes to that of lymphocytes, that is, the monocytic-lymphocytic ratio, often proves of invaluable assistance in diagnosis. In active tuberculosis the monocytes are markedly increased, and there is a reversal of the monocytic-lymphocytic index. In arrested tuberculosis there is an increase in the lymphocytes, with the total number of monocytes increased but less in number than the total lymphocytes. It has also been shown that there is a storehouse for monocytes in the tuberculous subject, which does not exist in the normal nontuberculous subject. If the total number of monocytes and the monocytic-lymphocytic ratio is determined before and after the administration of tuberculin subcutaneously, the blood of patients in which a definite focal reaction is obtained will show a marked increase in the number of monocytes and a shift in the monocyte-lymphocyte ratio. This simultaneous provocation of focal reaction and increase in circulating monocytes is strong evidence of the presence of tuberculosis.

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PROGNOSTIC VALUE OF BLOOD CULTURE IN TYPHOID FEVER AT VARIOUS PERIODS OF THE DISEASE.

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The earlier classics by such authorities as Curschmann,[4] Dieulafoy,[5] Grisole,[6] Jaccoud,[7] Laveran and Teissier,[8] as well as the modern by such well-known authors as Masters,[9] Anders,[1] Rogers,[11]

Cecil,[3] Rolleston,[12] Osler and McCrae,[10] and Castellani and Chalmers,[2] have all emphasized the importance of complications in the prognosis of typhoid fever, but no mention has ever been made of the prognostic significance of blood culture taken at different periods in the course of the disease.

It is the purpose of this paper to study this particular problem which ought to be of some practical value in medical practice.

The clinical records of the Philippine General Hospital from the years 1911 to 1931, inclusive, and of the San Lazaro Communicable Disease Hospital from the years 1927 to 1931, inclusive, furnish the materials for this study. During these periods a total of 5373 typhoid cases were admitted in these 2 institutions. Of this number 1962 cases (36.52 per cent) had blood cultures taken only once during the course of the disease; of these only 544 (27.73 per cent) were positive.

It is common practice among physicians to have blood cultures taken on typhoid suspects during the early period of the course of the disease only for purposes of diagnosis. It is, therefore, unusual to have blood cultures taken in unmistakably frank clinical cases of typhoid and more especially in the later stages of the disease. Furthermore, the majority of the typhoid cases among Filipinos were admitted to the hospital after the first week of illness. These conditions are responsible for the relatively few cases in which blood cultures were made.

The results of the above-mentioned study are presented in the following tables based upon the date when the blood culture was reported; but subsequent studies, based upon the date when the blood of the same group of cases was taken for culture, gave practically the same results:

TABLE 1.—TYPHOID FEVER FATALITY AT DIFFERENT PERIODS IN THE COURSE OF THE DISEASE IN CASES WITH POSITIVE AND NEGATIVE BLOOD CULTURE COMPARED.

Week.	Positive blood culture.				Negative blood culture.			
	Recovered.	Died.	Total.	Fatality rate, per cent.	Recovered.	Died.	Total.	Fatality rate, per cent.
1st	46	11	57	19.29	123	16	139	11.51
2d	168	74	242	30.57	585	85	670	12.69
3d	98	51	149	34.22	336	48	384	12.50
4th	39	22	61	36.06	103	22	125	17.60
5th	13	13	26	50.00	59	8	67	11.94
6th	3	3	6	50.00	12	1	13	7.69
7th and over	1	2	3	66.66	15	5	20	25.00
Total	368	176	544	32.35	1233	185*	1418	13.05

* Of this number, 104 cases were verified by autopsy.

TABLE 2.—TYPHOID FEVER FATALITY IN VACCINATED AND NONVACCINATED PATIENTS HAVING POSITIVE AND NEGATIVE BLOOD CULTURES AT DIFFERENT PERIODS OF THE DISEASE COMPARED.

Week.	Nonvaccinated.								Vaccinated.							
	Positive blood culture.				Negative blood culture.				Positive blood culture.				Negative blood culture.			
	Recovered.	Died.	Total.	Fatality rate, per cent.	Recovered.	Died.	Total.	Fatality rate, per cent.	Recovered.	Died.	Total.	Fatality rate, per cent.	Recovered.	Died.	Total.	Fatality rate, per cent.
1st	32	10	42	23.80	95	16	111	14.41	14	1	15	6.66	28	0	28	0.00
2d	137	67	204	32.84	472	77	549	14.03	31	7	38	18.42	113	8	121	6.61
3d	83	42	125	33.60	281	45	326	13.80	15	9	24	37.50	55	3	58	5.17
4th	34	22	56	39.28	83	20	103	19.42	5	0	5	0.00	20	2	22	9.09
5th	13	13	26	50.00	52	8	60	13.33	0	0	0	0.00	7	0	7	0.00
6th	3	3	6	50.00	10	0	10	00.00	0	0	0	0.00	2	1	3	33.33
7th and over	1	2	3	66.66	13	3	16	18.75	0	0	0	0.00	2	2	4	50.00
Total	303	159	462	34.41	1006	169	1175	14.38	65	17	82	20.73	227	16	243	6.58

Cases with positive blood cultures (Table 1) tend to present a higher fatality rate than those with negative blood cultures. While the fatality rate in cases having negative blood cultures remains almost at the same level at different periods in the course of the disease, the cases with positive blood cultures consistently demonstrate an increasing fatality as the period of the disease progresses.

It is well known that there is an early septicemia in typhoid fever which tends to disappear with the advance in the course of the disease. It is reasonable, therefore, to observe that the longer the typhoid organisms persist in the blood stream, the more unfavorable the consequence is for the patient. Presumably also a heavier infection has taken place in cases with positive blood culture than in those negative cases in the same stage of the disease. The protective mechanism of the body should be able to dispose of the bacilli more readily in the latter group of cases. Therefore, the significant difference of 19.3 ± 3.91 per cent in the total fatality rate between the groups with positive and those with negative blood cultures, respectively, should not be at all surprising.

Grouping the cases into the vaccinated and the nonvaccinated by different stages of the disease, it appears that in the nonvaccinated patients the fatality is much higher in cases with positive blood culture (34.41 per cent) than in those in which the organisms were not found in the circulation (14.38 per cent). It is also noticeable that a consistent rise in fatality at different periods in the course of the disease occurs among those from which the organisms were isolated from the blood stream, as contrasted with an almost uniform fatality curve of the negative blood culture cases. The difference in fatality between these two groups of cases amounts to 20.03 ± 4.51 per cent, the significance of which may not be ignored statistically.

The fatality difference between the total cases with positive and those with negative blood cultures, respectively, among the vaccinated groups is 14.15 ± 29.42 per cent. It is apparent that the data in these groups of cases are too meager to furnish enough material to constitute an adequate sample.

Summary and Conclusion. Of 5373 typhoid cases, only 1962 (36.52 per cent) had a single blood culture taken during the course of the disease for diagnostic purposes only, and of the cases with blood culture, 544 (27.72 per cent) were positive.

On the whole a typhoid case with negative blood culture is likely to present a more favorable outlook than one with organisms in the blood stream, especially after the first week of the disease.

The longer the typhoid bacilli persist in the circulation the more does the termination of the case tend to be fatal.

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DOUBLE BACTEREMIA (STREPTOCOCCUS VIRIDANS AND STAPHYLOCOCCUS AUREUS) DIAGNOSED BEFORE DEATH.

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Cases of bacteremia in which blood cultures have been found positive during life for S. viridans and S. aureus must be extremely rare, judging from the few reports in the literature. Mixed cultures from the heart's blood at autopsy are of course more common. Epstein and Kugel[1] in 1929, reporting the occurrence of but 2 cases of mixed infection with streptococcus and staphylococcus in 52 positive autopsy cultures, attributed these findings to an agonal invasion. In 1916 Warren and Herrick[2] in a survey of 134 cases of bacteremia included 7 cases of mixed infection, in 1 of which the S. hemolyticus and the S. aureus were isolated from the blood of a patient suffering with chronic otitis, mastoiditis and appendicitis.

This patient recovered following an appendectomy. The high virulence and rapid growth of S. aureus in the blood usually leads to a rapidly fatal outcome. Clawson[3] mentions the incidence of a S. aureus infection superimposed on an old healed valvular lesion. There is the possibility, as indicated by Thayer,[4] that the staphylococcus is preëminently a terminal invader. However, he does not clearly define his concept of a terminal invasion. Horder[5] lists 1 case in which a streptococcus and a staphylococcus produced an endocardial inflammation, but gives no further details. Libman[6] mentions a case in which a healing streptococcic endocarditis was secondarily invaded by S. aureus.

Case Report. The patient, J. K., a well-nourished female, aged 13 years, became ill on June 18, 1932, 3 days before being admitted to the Jewish Hospital. She complained of general malaise and arthralgia, and excruciating pain in the third toe of her right foot. The next day she had a severe chill followed by a sharp rise in temperature. Many petechial spots soon appeared on the abdomen, thighs, legs and arms, quickly increasing in size and prominence, many coalescing and forming large purplish blotches.

Her *past history* was significant. She had an attack of rheumatism at 5 years of age, all of her large joints being involved. Her tonsils were removed at 6; the appendix at 10 years of age. At 11 a second attack of rheumatism occurred, the duration of which was not recalled. The history was otherwise negative.

Physical Examination (June 21). The patient, a well-developed girl, was apparently very toxic. Her temperature was 105.4° F., and the pulse and respiratory rates were 120 and 22 respectively. The left border of her heart reached the anterior axillary line. A systolic mitral murmur was heard at the apex and a diastolic murmur at the third left interspace parasternally. Lungs and abdomen were essentially negative, the spleen and kidneys were not palpated. The patient's body surface presented multiple scratch marks and petechiæ. The right middle toe and the distal phalanx of the left little finger appeared gangrenous. There were no abnormal neurologic signs.

Progress. For a period of 7 days following admission her temperature remained elevated (between 102° and 105° F.) in spite of the administration of large doses of salicylates. Repeated showers of petechiæ were observed on the skin of the body and on the conjunctivæ. Epistaxis occurred once. Many hyaline and granular casts were constantly present in the urine. Meningism was observed 4 days before death. The spinal fluid examination was negative. Five days after admission harsh breath sounds and impairment of the percussion note were detected over the base of the left lung suggesting the onset of pneumonia. Two days before death she displayed a marked edema of the lower extremities. Death occurred on the 11th day of the disease and the 8th day of her stay in the hospital.

Laboratory Findings: June 21, 1932. Blood: Red blood cells, 3,450,000; hemoglobin, 63 per cent; white blood cells, 9000, with 70 per cent neutrophils. Platelets, 135,000. Blood sugar, 150 mg.; chlorids, 600; urea, 20. Urine: specific gravity, 1012. Many hyaline and granular casts.

The Widal reaction on 2 examinations was negative for typhoid and paratyphoid A and B. Agglutination for bacillus abortus, negative.

On June 22, an Roentgen-ray examination of the chest showed the cardiothoracic ratio (transverse diameter of heart-chest) to be 14.3/25 cm. (57 per cent). The lungs were negative except for an intensification of the

root shadows and a dense haziness at the extreme base on the left side. The electrocardiogram was essentially negative.

Blood cultures on June 27 and 28 were positive for the S. aureus. A second culture on June 28 was positive for S. aureus and also for S. viridans. On June 28 a blood culture which had been taken on June 26 was reported as positive for S. aureus and S. viridans. Approximately 185 colonies of the former and 25 colonies of the latter organism were reported as present in each cubic centimeter of blood.

Autopsy (Dr. B. A. Gouley) revealed numerous fine petechiæ over her entire body. The panniculus adiposus showed occasional petechiæ.

The *heart* weighed 360 gm. The epicardium was smooth. There was hypertrophy and dilatation of the left ventricle due to a long established chronic aortic valvulitis (rheumatic). The anterior leaflet of the mitral valve contained a friable vegetation the size of a ten-cent piece which had ulcerated mostly on the auricular side. Both coronary arteries were plugged along their middle course by brownish-gray emboli similar in character to the vegetation on the mitral valve. The absence of inflammatory reaction here pointed to the probable immediate cause of death.

Smears from the heart valves taken at autopsy showed such a predominance of staphylococci that it was extremely difficult to detect the few streptococci that were present.

Lungs. The diffuse mottling of congestion was observed with emphysema of the upper lobes, but no actual consolidation was noted. *Intestines* showed numerous petechiæ beneath the serosal surface. *Spleen, liver* and *kidneys* revealed many recent septic infarctions.

Pathologic Diagnosis. Double bacteremia. Widespread petechial and purpuric rash. Cardiac hypertrophy and dilatation. Rheumatic aortic valvulitis with regurgitation. Malignant (ulcerative) endocarditis of the mitral valve. Lungs: Congestion; mild emphysema. Adrenals: Lipoid exhaustion. Spleen: Congestion, hyperplasia, septic infarction. Kidneys: Septic infarction, congestion. Liver: Septic infarction, congestion. G. I. Tract: Petechiæ.

Conclusions. 1. Mixed bacteremias with the presence of S. viridans and S. aureus are rare and, when they do occur, tend to be fulminating in character.

2. Such mixed infections are particularly difficult to diagnose from blood cultures because of the multiplication of the staphylococcus in the blood stream to such a rapid degree that the sparse growth of S. viridans on culture media is recognized with difficulty.

3. In patients suffering with a proven S. viridans infection of the blood stream when the disease displays fulminating characteristics, bacteriologic search should be assiduously made for the presence of a mixed staphylococcus infection.

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A NOTE ON THE EFFECT OF CHLORINATED SWIMMING-POOL WATER ON FUNGI OF TOE RINGWORM.

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Ringworm of the toes (athlete's foot, dermatophytosis, etc.) has become a hygienic problem in all phases of gymnasium activity. The frequency among students has been adequately demonstrated by Hulsey and Jordan,[1] Legge, Bonar and Templeton[2] and others.

Definite prophylactic procedures have been recommended by Gould,[3] who advocated 10 to 15 per cent sodium thiosulphate foot baths, and by Osborne and Hitchcock,[4] who favored sodium hypochlorite. The latter workers indicated that a concentration of 0.1 per cent applied for a period of 1 minute was necessary in the test tube to kill fungi (Trichophyton interdigitale) representative of the disease in question.

Author's Tests on Fungus in Vitro. Numerous scrapings from a patient who yielded large quantities of fungus on microscopic examination were selected for the tests and their viability proved in cultures. Portions of the scrapings were soaked in water from the swimming pool and kept at warm room temperature. The pool water for this experiment was collected just before noon on Wednesday, January 27, 1932. On this day at 1 P.M. the chlorin concentration was 0.4 part per million at 76° F. Twenty-four girls had used the pool prior to the collection of the sample.

At 30-minute intervals numerous particles were removed from the solution and cultured. They remained positive after exposures to the chlorinated water of ½ hour, 1 hour and 1½ hours. There was not any growth either after 2 hours' or after 17 hours' exposure.

As recently reported by Templeton *et al.*,[5] this method, employing fungus in tissue as against fungus in culture material, is more representative of natural conditions. As far as can be deduced from this very limited observation on 1 patient,* the chlorinated water of our swimming pool was a fairly efficient fungicide for infectious material which might become detached from the feet of swimmers.

Conditions between the toes are not parallel with those in the test tube or in the swimming pool, being complicated by (1) the accessibility of the disinfectant to the interdigital spaces, and (2) depth of fungus in the skin. Accordingly, 6 women students

* The particular fungus species concerned in this test subject, Trichophyton interdigitale, was the one almost invariably encountered in the students at this university (73 out of 75 cultures).

attending swimming-pool classes during January and February, 1932, at this university were selected from 254 who had been examined and classified in respect to the presence of toe ringworm. The details of this classification will be found in another place (Gilman, Spring and Rea[6]). For the purposes of this note, it is sufficient to state that the 6 selected were from 15 instances of infection from which pathogenic strains of toe ringworm species had been obtained.

In testing the effect of chlorination, scrapings were obtained from the toes of the 6 students immediately before the regular 30-minute swimming period and again at its conclusion. The accompanying table indicates the results, namely, that the chlorinated water was not adequate to kill the fungus between the toes. It might be added that an interval of up to 16 hours sometimes elapsed between

Occurrence of Fungus Between Toes at Swimming Period.*

	Before.		After.	
Student No.	Microscopic examination.	Cultures.	Microscopic examination.	Cultures.
1	+	+	+	+
2	++++	+	++++	+
3	++	+	++	+
4	++++	+	++++	+
5	++++	+	+	+
6	+	−	+	+

* Fungus had been demonstrated by culture from the toes of all of these women on a previous occasion.

collection of materials and culture, thus giving additional time for the chemical to act. Furthermore, all of these women had been in regular attendance at the swimming pool for a several weeks' interval between the first identification of the fungus and the final set of tests. This gave yet further opportunity for the chlorinated water to exert fungicidal effects between the toes, had it possessed any.

Summary. Ringworm of the toes is such a problem among students and gymnasium habitués in general that a possible fungicidal rôle of chlorinated water in swimming pools merits testing. With 6 women swimmers as test objects, it appeared that:

1. It is possible for detached particles of ringworm tissue to retain viable fungi in chlorinated swimming-pool water for 1½ hours. The fungi, however, may be destroyed in 2 hours.

2. Chlorinated water in swimming pools does not effectually reach and kill fungus between the toes during an average 30-minute swimming period.

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DENTAL INFECTION AND SYSTEMIC DISEASE.*

A Review of the Literature and a Study of 883 College Students, Including Complete Dental Roentgen-ray Examination.

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Dental infection is older than the human race. In animals evidences of caries and of pyorrhea alveolaris have been found in the fossilized remains of primitive vertebrates of the Paleozoic era.[1] In both ancient and prehistoric human remains, evidences of alveolar abscesses and other dental infections have been found,[2] these being associated in some instances with arthritis deformans, and in others with spondylitis and osteitis.[3] The first written notice of oral infection as a cause of systemic disease is said to occur in the writings of Hippocrates,[1] and occasional references to the simultaneous occurrence of oral and systemic disease are to be found in the works of many ancient and medieval writers.

In 1809 Benjamin Rush[4] wrote, "I cannot help thinking that our success in the treatment of all chronic diseases would be very much promoted by directing our inquiries into the state of the teeth in sick people, and by advising their extraction in every case in which they are decayed. It is not necessary that they should be attended with pain in order to produce disease . . ." In 1889 and 1891 Miller[5,6] published his articles on oral infection, the term "focus of infection" being used in the title of his American contribution. In 1901 Hunter's[7] book on pernicious anemia expounded the view that this disease is due to infection of the stomach, which, in turn, is generally due to oral sepsis "arising in connection

* Published simultaneously in the American Journal of the Medical Sciences and Dental Cosmos, which reproduces illustrations omitted here.

with long continued and neglected cario-necrotic conditions of the teeth." Many modern workers including Moorehead,[8] Irons,[9] Hartzell[10] and Pemberton[11] have added their observations to show the concurrent existence of dental and systemic disease.

In 1911 Goadby[12] succeeded in producing a "condition indistinguishable from arthritis deformans" by the inoculation of cultures from infected teeth directly into the joints of 18 rabbits. Rosenow[13] has reported the occurrence in experimental animals of gastric ulcer, nephritis, nephrolithiasis, epidemic hiccup and other conditions following the intravenous injection of cultures from infected teeth, and he has also reported the production of these diseases in dogs by amputating the crowns of the teeth, exposing the dental pulp chambers and inoculating the latter with organisms cultured from human foci of infection or from the distant lesions which are presumed to have been caused by these foci. Other reports have been published corroborating Rosenow's work, but there are many authorities who maintain a skeptical attitude toward these researches.

Evidence of another kind, rather unconvincing in character, has had considerable influence in furthering the theory that dental infection may cause rheumatism and arthritis. It consists in the demonstration of nonhemolytic streptococci in the dental lesions of patients suffering from rheumatism or arthritis. It may be regarded as established, however, that nonhemolytic streptococci are to be found in the saliva and about the teeth of normal persons throughout life: that they may usually be cultivated from the roots or the pulps of devitalized teeth, and occasionally from those sites in vital and apparently healthy teeth: finally, that the so-called blind abscess, or chronic rarefying osteitis with granulation tissue, usually yields cultures of nonhemolytic streptococci, though many are found to be sterile. The nonhemolytic streptococcus may be said, therefore, to be a common inhabitant of the human mouth, both in health and in disease. The demonstration of an organism of this group in the dental lesions of patients suffering from arthritis should, therefore, not be given too great emphasis.

Nonhemolytic streptococci have also been reported by Cecil, Nicholls and Stainsby[14] in the blood of arthritic patients with significantly greater frequency than in a control group. Since, however, other workers[15,16] have been unable to corroborate these findings, it will probably be best for the present to maintain an open mind as to the streptococcic etiology of arthritis deformans.

That disappointing results frequently follow the removal of foci of infection was observed by Billings,[17] one of the earliest and most enthusiastic adherents to the focal infection theory. To explain these failures, he advanced the hypothesis of the implantation of organisms into the synovial tissues themselves, which then became secondary foci of infection. However plausible this theory may be,

it lacks proof. Moreover, numerous writers[1,11,18,19] have reported the occurrence of rheumatism and arthritis in the absence of any of the ordinarily recognized foci of infection.

Pemberton,[20] in his study of 400 arthritic soldiers, writes: "184 patients, or 46 per cent, recovered in the presence of demonstrable surgical foci. This is nearly 3 times the number which improved (65 cases, or 16.25 per cent) after the removal of foci." Mutch,[18] Miller,[19] Badanes,[1] and Broderick[21] also minimize the importance of dental infection in arthritis, and it is, indeed, common knowledge that many cases of arthritis recover in the presence of demonstrable infection in the teeth and elsewhere, whereas many fail to recover after the most thorough removal of all possible foci.

Another aspect of the focal infection theory which has impressed some writers has been the statistical evidence of the coincident occurrence of abscessed teeth and chronic disease, especially arthritis. The revelation by Roentgen ray of dental infections previously unsuspected has greatly stimulated interest in this subject. Thus Moorehead,[8] Irons[9] and Pemberton and Robertson[22] found periapical dental infection in 89, 76, and 33.5 per cent respectively of their arthritis cases. The mere demonstration of the frequent association of dental infection and arthritis does not, of course, indicate a causal relationship between the two conditions. Not only is it conceivable that the dental sockets, being actually joints, might themselves present rheumatic or arthritic manifestations,[23] but it is also possible that certain conditions might exist which would exert an adverse effect upon both the joints and the teeth. The most obvious factor of this nature is that of age. Moorehead,[8] Duke[24] and others have shown that with advancing age there is a marked increase in the incidence of dental infection. Black[25] believes that almost 100 per cent of persons over 50 years of age have such infection present. It is not surprising, therefore, to find a higher incidence of dental infection in arthritis, a disease of later life, than in diseases to which the young are most susceptible. It should not be forgotten, moreover, that dental infection is very prevalent in patients with diverse diseases: thus Thoma,[2] Duke,[24] Moorehead,[8] Haden,[26] Pemberton,[27] and Irons,[9] report its presence respectively in 88, 81, 74, 68, 58, and 44 per cent of medical cases of various sorts. Its presence in arthritis is found by Moorehead, Irons and Pemberton respectively to be 89, 76 and 33.5 per cent, which therefore is within the range of its reported incidence in unselected medical patients. One may conclude, therefore, that although dental infection is common in arthritis it is by no means limited to this or to any other chronic disease, and that the coincident existence of arthritis and dental infection does not offer any proof of a causal relationship between the two.

Appleton,[28] reviewing the records of drafted men during the World War, showed by the use of semi-logarithmic graphs that

recruits exhibiting dental disease did not show an undue incidence of arthritis, appendicitis, gastric ulcer, endocarditis, osteitis deformans, myositis or muscular rheumatism. A weakness in this method of approach, as pointed out by the author, lies in the variable diagnostic criteria used by the different examiners. Moreover, an ordinary clinical examination of the teeth could not be expected to reveal all or even most of the dental infection present. To secure the best possible data, a complete dental Roentgen ray, as well as a careful clinical, dental and medical examination would be required. A dental examination of this kind correlated with a physical examination on a sufficiently large number of individuals to be of statistical value does not appear to have been recorded in the literature up to the present. Black[25] made complete dental Roentgen rays on 175 dental students and 225 dental patients, accompanied by a questionnaire into the health of the 400 subjects; but the health findings are not correlated with the dental findings. Hyatt,[29] of the Metropolitan Life Insurance Company, made radiograms of 2787 bridged and devitalized teeth, and reported a high incidence of root lesions; but these results were also not correlated with any medical findings. We believe, therefore, that the present study on 883 students is the first of its kind to appear in the literature.

Medical and Dental Study.* The material upon which this study is based consists of 883 students of Drexel Institute, a small college located in the center of Philadelphia. As regards economic and social status, the group represents a well-to-do but not a wealthy class, many students having to work their way through college. Of the 883 students studied, 502 (56.9 per cent) were males and 381 (43.1 per cent) were females. The average age was 18.75 years, the modal age was 18 years, and the great majority fell between the ages of 16 and 21 years (Table 1).

TABLE 1.—SEX AND AGE OF SUBJECTS.

Age.	Women.	Men.	Total.
16	9	12	21
17	76	83	159
18	158	153	311
19	67	100	167
20	26	73	99
21	6	29	35
22	6	27	33
23	3	14	17
24	1	5	6
25	0	2	2
Over 25	5	4	9
Age not stated	24	0	24
Total	381	502	883

* A brief résumé of the dental findings including Tables 2, 3, 4, 5 and 8 appeared in the Proceedings of the Twelfth Annual Meeting of the American Student Health Association, December, 1931, p. 90.

The physical admission requirements are essentially the same as those of other American colleges. Students are excluded because of physical disabilities only when the latter are serious enough to be incompatible with the fulfillment of academic duties, or when they are a menace to health. No cases of arthritis deformans have been recognized among the students during the period of this study (1929 to 1931, inclusive); but, of course, it is impossible to ascertain whether any prospective students were prevented from becoming candidates for admission because of this, or any other disease. In this respect, all that can be said of this group is that it is a representative sample of students, drawn from a typical American city and its surrounding territory. Completeness of records furnished the only criterion for inclusion or exclusion in this study. Most of the students were freshmen, though a few belonged to the upper classes or were graduate students.

The method of study consisted in taking a medical history and physical examination, including a urinalysis. The dental examination was by a competent dental student or by a graduate dentist, and a Roentgen ray film was made of every tooth and edentulous space (10 films for each case). All dental films were read by the same dental roentgenologist (L. M. E.).

The findings of greatest importance, both from the standpoint of frequency and of oral hygiene, are those relating to dental caries. A tooth containing an area of decay, a leaky filling or an unfilled cavity is regarded in this study as carious. Neglected caries is responsible for most of the teeth prematurely lost by the human race. This fact alone makes caries the most important of all dental conditions.

Caries was found with surprising frequency in our study (Tables 2 and 3). Many carious teeth which had not been detected by clinical examination were revealed by the Roentgen ray; and the reverse was also frequently true. This was demonstrated by the fact that 1662 teeth were found carious by clinical examination and 1372 by Roentgen ray; but of these there was agreement only in the case of 237 teeth. In other words 1425 teeth found carious clinically failed to show caries by Roentgen ray, while in 1135 teeth the reverse was true. Therefore, had the teeth been examined without the aid of the Roentgen ray, 1135 carious teeth (40.6 per cent of the entire number) would not have been detected.

TABLE 2.—THE FREQUENCY OF DENTAL CARIES AS DETERMINED BY COMBINING CLINICAL AND ROENTGEN RAY FINDINGS.

Number of students examined	883
Number of students showing caries	733
Per cent of students showing caries	83
Approximate number of teeth examined	27,398
Number of teeth with caries	2,797
Per cent of teeth showing caries	10.3
Average number of carious teeth per student	3.2

Here and in the tables which follow, regardless of the number of cavities in the tooth, it was counted as but one carious tooth. Sound filled teeth are not included.

TABLE 3.—THE OCCURRENCE OF DENTAL CARIES PER STUDENT AS DETERMINED BY COMBINING CLINICAL AND ROENTGEN RAY FINDINGS.

	No. of students.	Per cent.
No carious teeth	150	17.0
Caries in 1 tooth	131	14.9
Caries in 2 teeth	157	17.9
Caries in 3 teeth	121	13.7
Caries in 4 teeth	98	11.1
Caries in 5 teeth	71	8.0
Caries in 6 teeth	48	5.4
Caries in 7 teeth	39	4.4
Caries in 8 teeth	25	2.8
Caries in 9 teeth	11	1.2
Caries in 10 teeth	2	0.2
Caries in 11 teeth	13	1.5
Caries in 12 teeth	9	1.1
Caries in 13 teeth	4	0.4
Caries in 14 teeth	2	0.2
Caries in 15 teeth	1	0.1
Caries in 16 teeth	1	0.1
Total number of students	883	

Theoretically, a tooth with caries which involves either the dentin or the pulp, may act as a focus of infection. Bacteria may be cultured even from unexposed areas of dental caries. The dental artery and vein enter the tooth through its apical foramen and send their branches throughout the pulp. The dentin communicates with the pulp by numerous minute canals, so that microorganisms, or their toxic products, could conceivably find their way from the dentin to the pulp and thence into the systemic circulation, leading to disturbances in distant parts of the body. If such were frequently the case we should expect in this group of students to find a high incidence of those diseases which are due to focal infection. Actually, however, no cases of arthritis were encountered, and the incidence of rheumatism, heart trouble or chorea was not significantly higher in the students with demonstrable caries than in those without. Of the group whose histories stated that they had had rheumatism or chorea since early childhood, or whose cardiac examination revealed evidences of valvular heart disease, 85 per cent had carious teeth, the average number of carious teeth per student being 3.3. In the group with a negative history of rheumatism or chorea and without valvular heart disease, 82.6 per cent had carious teeth, the average number of such teeth per student being 3.2. These differences are too small to be regarded as significant, and it may be said that the data offer little support for the assumption that caries is a frequent cause for these 3 diseases.

The findings of greatest importance as regards focal infection relate to the incidence of dental granulomata. Granuloma is the synonym for chronic rarefying osteitis with granulation tissue, the so-called but misnamed chronic root abscess of medical parlance. Granuloma was found in 19.8 per cent of the students examined

(Table 4). This lesion is regarded by the majority of physicians and dentists as potentially a dangerous focus of infection. It can be detected only by means of the Roentgen ray though it can sometimes be surmised to be present by clinical examination. A question of considerable importance is whether it is possible to predict from the appearance of a tooth that its root will be found to be the seat of chronic rarefying osteitis with granulation tissue. Obviously, if such a condition can be predicted from a clinical examination, then a complete Roentgen ray examination is of less importance. Table 5 throws considerable light upon the relation of such clinical predictions to facts as revealed by the Roentgen ray. Of 232 proved granulomata, 106 (45.2 per cent) were suspected from the clinical appearance of the teeth. In other words, if only the suspicious teeth had been Roentgen rayed, 126 or over a half of the granulomata would have been missed. On the other hand, 495 teeth presented a suspicious appearance clinically, but were exonerated by the Roentgen ray: thus out of every 6 predictions of granuloma, approximately 1 proved to be correct. Often clinically innocent looking teeth showed granuloma by Roentgen ray, and often dangerous looking teeth presented a normal Roentgen ray appearance at the roots, so that the conclusion seems justified that a dental examination is not complete without a full mouth Roentgen ray. Even the edentulous spaces should be Roentgen rayed, as had been emphasized by Eusterman.[30]

TABLE 4.—THE FREQUENCY OF GRANULOMA AS DETERMINED BY ROENTGEN RAY.

Number of students examined	883
Students showing granuloma	175
Per cent of students showing granuloma	19.8
Approximate number of teeth examined	27,398
Number of teeth showing granuloma	232
Per cent of teeth showing granuloma	0.8

Here, and in the tables which follow, the term granuloma is synonymous with chronic rarefying osteitis with granulation tissue, the so-called chronic root abscess or blind abscess of medical parlance.

TABLE 5.—GRANULOMA. COMPARISON OF CLINICAL AND ROENTGEN RAY FINDINGS, SHOWING THE RESULTS OF ATTEMPTING TO PREDICT THE PRESENCE OF GRANULOMA FROM THE CLINICAL APPEARANCE OF TEETH.

	Students.	Teeth.
1. Granuloma suspected clinically; found by Roentgen ray	91	106
2. Granuloma not suspected clinically; found by Roentgen ray	100	126
3. Total number of granulomata (1 plus 2)	232	
4. Granuloma suspected clinically; not found by Roentgen ray	333	495
5. Per cent of proved granulomata suspected clinically	45.2	
6. Per cent of suspected teeth showing granulomata	17.6	

The records of the students exhibiting dental granulomata were compared with those without granulomata, to determine the correlation of granuloma with certain physical conditions suspected of being related to focal infection. First the students whose history

cards indicated that they had had rheumatism or chorea since early childhood, or who on examination were found to have evidences of valvular heart disease, were grouped together (Table 6). It was found that the incidence of the above named diseases was actually slightly lower in the students with dental granulomata than in the students without granulomata. This finding does not substantiate the view that granulomata played a significant part in the production of the chorea, rheumatism and valvular heart disease in this group. Nevertheless, one might still hold this view and explain the lack of correlation of rheumatism, chorea, and valvular heart disease with dental granulomata, on the assumption that in the case of the students with the above named diseases, the teeth had been Roentgen rayed at some prior time, and all those with granulomata removed. If such were the case, a higher incidence of missing teeth might be expected in this group than in the students without rheumatism, chorea or valvular heart disease. Such was not found to be the case. There were actually 1.11 missing teeth per student in the entire group studied, and 0.96 missing teeth per student in the 26 persons comprising the chorea, cardiac and rheumatic group.

TABLE 6.—THE ASSOCIATION OF CERTAIN PHYSICAL ABNORMALITIES WITH DENTAL GRANULOMA IN 883 STUDENTS.

	With dental granuloma.		Without dental granuloma.	
	Number.	Per cent.	Number.	Per cent.
Students	175		708	
Rheumatism, chorea, or heart trouble	5	2.9	21	3.0
Underweight (10 pounds or more below standard for height and age)	44	25.1	153	21.6
Albuminuria (albumin, from a trace to a cloud, with or without casts, found in 1 specimen of urine)	12	6.9	27	3.8

Next the records of the students who were found to be 10 pounds or more underweight for their age and height were considered. The incidence of leanness (10 pounds or more underweight) was 3.5 per cent greater in the students with granulomata than in those without (Table 6). Whether this difference is sufficiently large to be significant, can best be determined by employing statistical methods. It has become a convention to regard twice the standard deviation of simple sampling[31] as the minimum significant difference.* The observed 3.5 per cent is found to be 0.97 of its standard deviation;† and therefore, according to these criteria, too small to be significant. To state the matter a little differently: it has become conventional to regard a variation as not significant if there is a greater than 5 per cent probability of its occurrence being

* Three times the standard deviation is also used.[32]

† The formula employed was that of Yule,[33] namely: $\epsilon\frac{2}{12} = \frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}$

due to the fluctuations which may be expected between different samples of the same large group. The probability that the greater incidence of underweight in our granuloma group is due to such fluctuations is found to be about 33 per cent. One may conclude, therefore, that the increased incidence of underweight in the granuloma group is not large enough to indicate a significant association between granuloma and underweight.

Third, the records of the students with albuminuria were considered. Its incidence was 3.1 per cent greater in the group with granulomata than in the group without (Table 6). Although the difference noted was, in this instance, relatively greater with respect to its standard deviation than in the preceding instance, it does not quite fulfill our requirement for statistical significance, since it is but 1.5 times as great as the standard deviation, there being approximately a 13 per cent chance that such a difference is due to the fluctuations of sampling referred to in the previous paragraph.

TABLE 7.—INCIDENCE OF ELECTROCARDIOGRAPHIC CHANGES IN 160 WOMEN STUDENTS WITH AND WITHOUT DENTAL GRANULOMATA.

	With dental granuloma.		Without dental granuloma.	
	Number.	Per cent.	Number.	Per cent.
Women electrocardiographed	27		133	
Normal tracings	23	85.2	109	82
Tracings showing some departure from normal	4	14.8	24	18

TABLE 8.—MISCELLANEOUS ROENTGEN RAY FINDINGS.

	Students.	Teeth.
Missing teeth	419	896
Impactions	344	686
Residual roots	34	38
Chronic proliferative alveolo-dental periostitis	18	20
Root absorption	9	9
Condensing osteitis	7	7
Chronic rarefying osteitis with cyst formation	4	7
Horizontal absorption of alveolar process	3	3
Chronic rarefying osteitis with suppuration	2	2
Pulp nodules	1	3
Calcification of pulp	1	1
Hyperplasia of cementum	1	1
Fracture	1	1

Finally, the records of 160 women students, who had had electrocardiograms made as part of their routine examination, were analyzed with respect to the presence of granulomata. They were divided into two groups, normal and those departing in some respect from the normal. The latter group was composed of girls whose *Q–R–S* or whose *T* waves were below the accepted standards in Leads I or II, or both, who showed left axis deviation or who exhibited premature contractions. No evidences of grave myocardial damage were found in the group. An analysis of this

group showed that the incidence of electrocardiographic abnormalities was slightly greater in the group without granulomata than in the group with granulomata (Table 7). This result does not support the supposition that in these students granulomata produced electrocardiographic variations from the normal.

In addition to the presence of caries and dental granulomata a number of other dental conditions shown in Table 8 were revealed in the roentgenograms. From the standpoint of systemic disease, chronic rarefying osteitis with suppuration is the most important. This condition may result in osteomyelitis of the jaw, Ludwig's angina, and even fatal bacteremia, though none of these complications occurred in either of our 2 students.

Discussion. The data here presented were secured almost exclusively from youthful persons (Table 1), and should not be regarded as applicable to elderly individuals. While these data offer no support for the view that dental infection causes rheumatism, chorea, valvular heart disease, or electrocardiographic abnormalities in these vigorous young college students, yet, if the body resistance should be lowered by exposure, hardship or advancing years, it is possible that such might be the case. It is also conceivable that granulomata and other dental infections may, like syphilis, lie dormant for many years, finally to arise and smite their victims in later life. It would seem the part of wisdom, therefore, to treat these dental infections as potentially dangerous. This can often be done without the extraction of the affected teeth, it having been demonstrated that the majority of granulomata can be successfully treated through the root canal.[33] The wholesale removal of devitalized teeth and teeth with granulomata is certainly without justification in healthy young individuals such as comprise the present study.

Summary. 1. The literature upon the relationship of dental infection and systemic disease is reviewed.

2. The results of 883 routine medical and dental examinations, including complete dental Roentgen rays, are reported.

3. The Roentgen ray was found to be of great assistance in revealing caries, the latter being present in 83 per cent of the entire group.

4. Chronic rarefying osteitis with granulation tissue (the so-called blind dental abscess) was revealed in 19.8 per cent of the group. It often occurred with underweight and with albuminuria, but no statistically significant association could be demonstrated. It was not associated with rheumatism, chorea, and heart disease.

5. In 160 women students there was no association between the presence of chronic rarefying osteitis with granulation tissue and electrocardiographic abnormalities.

6. Several other roentgenologic abnormalities were found, the most common being impactions and residual roots.

7. The importance of routine dental roentgenograms as part of a thorough physical examination is emphasized.

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TRANSFUSION SYPHILIS.

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Recently Polayes and Lederer[1] reported a case of a child, aged 17 months, who had been infected with syphilis by blood transfusion, and collected 11 such cases from the literature. In addition to the reports cited by these authors, Fordyce[2] refers to a young girl who

had been infected in this way. Her brother, whose blood was used for the treatment of her anemia, was found to have been in the second incubation period of the disease at the time of the transfusion and in due course of time she had developed a secondary rash

On account of the relative infrequency of such published reports, it seems worthwhile to record the following:

Case Abstract. CASE 1.—Mrs. M. J., an undernourished negress, aged 34 years, presented herself to our dispensary on February 2, 1931, complaining of enlarged cervical glands. She stated that in October, 1930, after a miscarriage followed by severe hemorrhage and anemia, she had been given a transfusion of blood at another local hospital, her sister serving as donor.

When first seen the patient complained of severe headache, which she said had been present since the transfusion. Two weeks later she returned to the dispensary with a generalized corymbose papulopustular eruption. Her blood showed a strongly positive Wassermann reaction. Careful examination revealed no genital or extragenital lesion on either the patient or her husband. The husband's blood gave an entirely negative Wassermann reaction.

The records of the hospital at which the transfusion was given showed that while the donor's blood had been typed, a Wassermann reaction had not been done. After considerable difficulty we induced the obviously reluctant donor to submit to a blood test and the Wassermann reaction was found to be strongly positive.

While her eruption was still present, the patient was presented at a meeting of the Cleveland Dermatological Society with general agreement as to the diagnosis. In the discussion, verbal report was made of two other instances of transfusion syphilis, while a paper read later to a small medical group elicited mention of 4 additional cases. At the first meeting, Dr. H. T. Phillips, of Wheeling, West Virginia, referred to a threatened malpractice suit, which had been settled out of court, because of a syphilitic infection as a result of transfusion.

CASE 2.—In 1929, I was asked to testify about a syphilitic infection allegedly produced by transfusion. It appeared that the patient had been brought to a local hospital 2 years before in a state of severe shock from postpartum hemorrhage. The attending obstetrician had used the patient's brother-in-law as a donor after obtaining a denial of venereal infection. The urgency of the emergency did not permit waiting for the results of a Wassermann test and the patient's husband was not in a suitable blood group. Three months later the patient appeared with a secondary syphilis. In the meantime, a Wassermann reaction had been done on the donor's blood, which was alleged to be positive. I did not have the opportunity to see the patient and the case was soon after stopped for legal reasons. The defense attorney informed me that there were no cases on record of malpractice suits on this score.

Accidents of this sort would introduce a nice question of justice, especially when it is remembered that transfusion is often carried out as a life-saving measure under emergency conditions and that any available donor may have to be used, relying solely upon the denial of venereal infection. Shall the medical attendant save the

patient's life by transfusing blood from an apparently suitable donor at the risk of syphilitic infection or shall he let the patient die because of inability to secure a Wassermann-negative donor in the emergency and fear of possible syphilitic infection? Is the physician not taking every reasonable precaution in a desperate emergency when he attempts to exclude syphilis by questioning the donor and examining the surface of his body and the oral cavity for evidence of healed or active lesions when the condition of the patient is so desperate that time cannot be lost in securing a donor with a negative Wassermann reaction or in having one done on the available donor?

The microprecipitation methods devised by Kline[3] would seem to offer the clinician ready assistance, and his finger blood precipitation test with "exclusive test antigen" should be especially useful when little time is available, judging by the results obtained by Eller and Rein.[4]

In reviewing the reported cases, it is evident that the time elapsing between transfusion and the appearance of the eruption, ranged from 1 month to 4 months, the longest interval being in the case herewith reported. In the majority, the time was 2.5 months or longer.

A preponderating number of cases were found to be due to family donors, as noted by Polayes and Lederer. The cases which have been recounted here, still further emphasize the necessity for caution in dealing with family donors. It should be remembered that even professional donors, on whose blood negative Wassermanns have been obtained periodically, cannot be regarded as entirely safe on that account alone, because of the possibility of a recent venereal infection, and this points to the desirability of at least a careful inspection of the body surface and especially the genitalia, before transfusion, even in professional donors with repeated periodic negative blood tests.

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OBSERVATIONS REGARDING KIDNEY FUNCTION TESTS IN ACUTE NEPHRITIS.

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It has been maintained that kidney function tests are of little or no value in acute nephritis, because when performed some time after the onset of the disease they generally show normal results,

whether the disease is cured or it has become chronic (Lundsgaard[1]). Hence we are in a difficult position when in a given case we are to settle the question between a cured acute nephritis and a chronic nephritis. The common chemical and microscopic examination of the urine does not give any definite clue, because on the one hand acute nephritis according to Volhard[2] may be cured in spite of a persisting albuminuria, which may not disappear for several years, and on the other hand the complete disappearance of albumin, casts and red blood corpuscles from the urine does not necessarily mean that the nephritis is cured. Donath[3] has observed 3 cases in which the Volhard concentration test showed pathologic results for some time after the urine had become normal and later became normal. Such cases do not seem to be frequent, but it must be remembered that it has not hitherto been common to perform functional tests in cases of acute nephritis when the urine has become absolutely normal.

These facts, that the nephritis may be cured in spite of persisting albuminuria and that the kidney function may be decidedly deficient in spite of the disappearance of all pathologic components of the urine, render the functional tests necessary in acute nephritis, and the best and finest will here be desirable. One cannot be sure that cases like Donath's would not have developed into chronic nephritis if treatment had been stopped, for instance 1 or 2 weeks after the urine had become normal. The ideal must be to treat these patients until they have both normal urine and normal function.

In this article I shall try to set forward the experiences with functional tests in 25 cases of acute nephritis. Almost all these cases have been followed with repeated functional tests from the onset of the nephritis. The functional tests employed have been the Volhard-Strauss test and chiefly the creatinin test in the form given by Rehberg[4] and the author, by which the "creatinin clearance" is determined, *i. e.*, the amount of blood plasma cleared of creatinin per time unit. For reasons discussed in earlier papers we consider the value $\frac{\text{Cr U}\%}{\text{Cr P}\%} \times \text{V}^* = \text{F}$ (*i. e.*, the amount of fluid filtered in the glomeruli per minute equals the amount of filtrate or the filtration rate). For further description of the method I must refer to earlier papers; I only want to add that the creatinin test can be employed without causing any harm to the patient, even in quite recent cases.

The Volhard-Strauss test has been performed in the manner described by Volhard. As this test involves drinking of considerable water, which may be harmful to the patient, it has not been done at a very early stage of the disease. As has been stated by several authors, the result of the water excretion and dilution test

* Cr U% means the concentration of creatinin in the urine of a given space of time; Cr P%, the concentration in the blood plasma at the same time, and V, the diuresis for this time.

is to a large extent depending on extrarenal factors. It is customary to put these patients on a rather limited fluid intake; this alone suffices to make the water and dilution test illusionary. The results of this part of the Volhard-Strauss test have, therefore, not been taken into consideration. The concentration test is, however, of considerable importance.

Further the blood urea has been determined at short intervals and the daily diuresis and specific gravity of the urine has been determined.

The material comprises 25 patients with acute glomerular nephritis treated in the Blegdamshospital in Copenhagen (fever hospital). They have, as already stated, almost all been followed from the onset of the nephritis. Most of the patients were sent to the hospital for an acute infection (scarlet fever, angina, etc.) and got nephritis while in hospital. Several of the patients were children. The normal amount of filtrate in these is, of course, different from that of adults. The minimum value can, however, be determined from the surface area of the child, which is easily computed by means of Du Bois[5] or Benedict and Talbot's[6] tables. I have shown that the minimum filtrate per square meter is 60 cc. per minute, the average being 83.3 cc. per minute.[7]

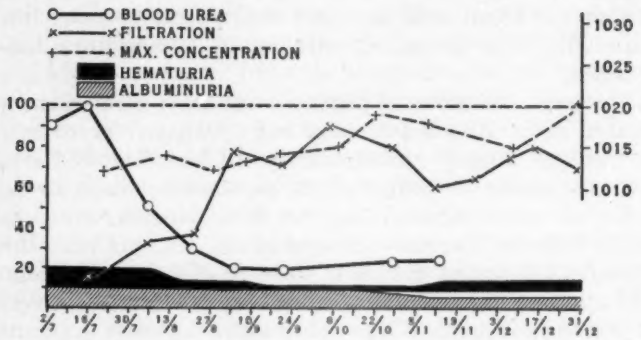
Acute nephritis may run a different course. There are three possibilities: (1) The disease passes into chronic nephritis (Volhard's second stage); (2) the disease is cured, the pathologic processes are entirely stopped and completely repaired (*restitutio ad integrum*); (3) in some cases albuminuria and hematuria may persist for some time and then disappear. Volhard speaks of "Defektheilung" or "Restalbuminurie." Even if in these cases a *restitutio ad integrum* has not taken place, Volhard is of opinion that no further development of the alterations in the kidneys which is the cause of these pathologic excretions takes place; this can, however, only be ensured by observation for a long time.

I will, by means of illustrating examples out of my material, endeavor to show the value of function tests in judging the course of a given case of acute nephritis and in settling the question whether the disease is cured or not.

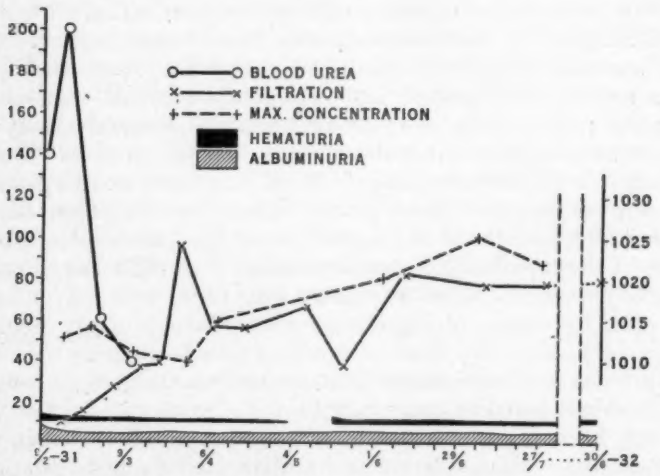
First, I want, however, to call attention to the fact that in most of these cases the albuminuria (positive Heller's test) disappears before the microscopic hematuria. The urine was examined for albumin once or twice a week and microscopic examination was carried out once a week. Only in 1 out of 25 cases did the erythrocytes disappear before the albumin; this case will be referred to later. In 2 cases the disappearance seemed to take place simultaneously, and in 19 cases the albumin first disappeared, in 1 case even 4 weeks before erythrocytes. Two cases became chronic and 1 case was regarded as recovered with "Restalbuminurie."

Curves 1 and 2 give the function tests in the 2 cases which became

chronic. The first curve is from a young man, aged 17 years, who had always been well until 2 days before entering the hospital, when he got a rather severe angina. On entrance to the hospital on June 26, 1930, he had marked albuminuria and hematuria, rather high blood urea and a very low filtration (14 cc. per minute



CURVE 1.—Acute nephritis developing into chronic. The function does not become normal. (— - — - — means the lowest normal filtration rate for a person of the patient's size.



CURVE 2.—Acute nephritis developing into chronic. Concentration power becomes normal. Filtration rate remains too low.

on July 16), with impairment of concentration power (maximum concentration 1013). His blood urea became normal rather quickly (within 5 weeks) and function improved; but not until after some 8 weeks did the filtration rise rather sharply to 80 cc. per minute and the concentration power to about 1015. But albuminuria and microscopic hematuria persisted and both the filtration rate and

the concentration power remained low even 6 months after the onset of the nephritis.

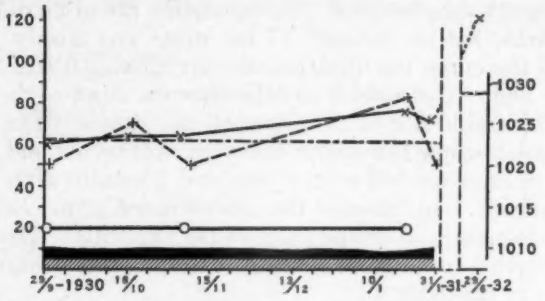
Curve 2 is derived from a young woman, aged 19 years, who never had been ill until she got erysipelas of the face (January 15, 1931), and was sent to the hospital. On admission the urine did not contain albumin, but on January 17 the urine was bloody. As it is seen from the curve the filtration was very low (9.5 cc.), the blood urea very high. Not until 2 months after the onset of the nephritis did a considerable rise of the filtration take place. The albuminuria and microscopic hematuria, however, still persist and the filtration test remains too low even 1 year and 5 months after the onset of the nephritis. In this case the concentration power became normal some 6 months after the onset of the nephritis. The filtration test thus seems to be more delicate than the concentration test. I shall refer to this later.

It will be observed that in both these cases the functional impairment is severe and a considerable improvement did not occur until relatively long time after the onset.

Curve 3 shows a case where the diagnosis "Restalbuminurie" was probable and later confirmed by reëxamination. It is from a boy, aged 9 years, who in November, 1929, had got angina and a consecutive acute hemorrhagic nephritis. Functional tests were not carried out until 10 months after the onset; hematuria and albuminuria were then still present. Filtration at that time was at the lowest normal level. It slowly improved, and when the boy was examined again on July 1, 1932, 2 years and 8 months after the onset of the nephritis, function was perfectly normal (128 cc.) and no albumin, erythrocytes or casts were to be found in the urine. In this case the diagnosis "Restalbuminurie" or "Defektheilung" proved to be right, but I want once more to emphasize that this diagnosis can only be accurately determined by observations over a long time.

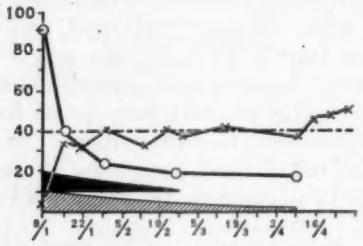
The next curve (Curve 4) shows this. The diagnosis "Restalbuminurie" was very tempting, but the filtration test shows that the nephritis was not cured until 4 to 5 weeks *after* the cessation of the microscopic hematuria. The patient was a little girl, aged 4 years, who had been ill for 2 months before entrance to the hospital. Albumin had been found in the urine after a cold. The urine was free from albumin when she got up 4 days before entering the hospital, but she immediately became ill again with very bloody urine and was sent to hospital on January 4, 1931. She was azotemic and the filtration rate was very low but rose rapidly. The blood urea quickly became normal. On February 26 no blood corpuscles were to be found in the urine but albuminuria persisted. The filtration rate was at the lowest normal level or a little lower. On April 9 the albuminuria stopped and the filtration rate showed a marked rise to values definitely above the lowest normal level.

In this case the functional test with creatinin proved to be of value in the differential diagnosis between "Restalbuminurie" and still existing nephritis.



CURVE 3.—"Restalbuminurie"—disappeared 2 years and 8 months after onset. — - — - — lowest normal filtration rate.

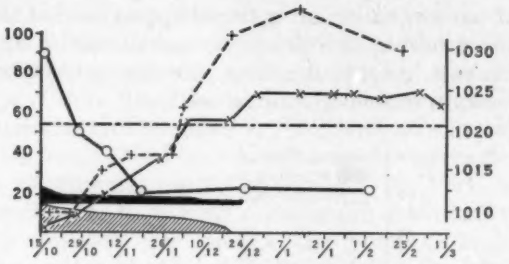
As mentioned before, albuminuria most commonly disappears before the microscopic hematuria. Function as determined by means of the creatinin test often becomes normal at the same time as the microscopic hematuria disappears. Curve 5, from a case of scarlet fever nephritis in a boy, aged 5 years, is an example of this.



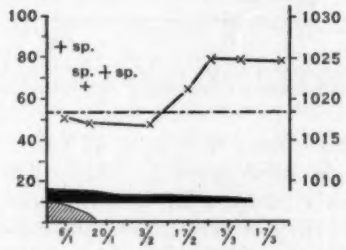
CURVE 4.—The filtration rate does not become normal until 4 weeks after the disappearance of red blood cells in the urine simultaneously with the disappearance of the albuminuria.

The concentration test gives normal results before the filtration rate is normal. A further example has already been given in Curve 2. Curve 4 is an example of a course which only was seen once in 25 cases, the erythrocytes disappearing before the albumin and function becoming normal simultaneously with the disappearance of the albuminuria. Another course which is very uncommon is shown in Curve 6, derived from another case of scarlet fever nephritis in a girl, aged 8½ years. In this case the albumin disappeared and a couple of weeks later the filtration rate became normal, but the microscopic hematuria persisted for another couple of weeks. Such a course I have only seen once. But a course which is by no means

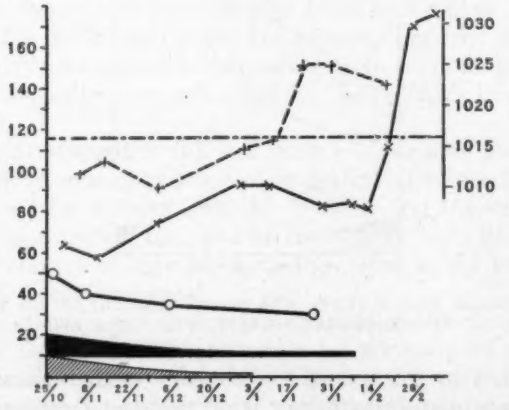
uncommon is seen in the 3 following curves. The first (Curve 7) is from an adult woman, aged 27 years. She came into hospital



CURVE 5.—The filtration rate becomes normal at the time when the hematuria disappears—a common course. Concentration power normal about 4 weeks before normal filtration has been reached.



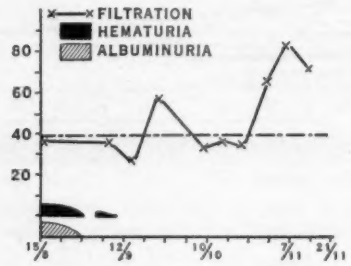
CURVE 6.—The filtration rate becomes normal before the hematuria disappears; sp. = spontaneous specific gravity of the 24-hour urine.



CURVE 7.—The filtration rate does not become normal until 14 days after erythrocytes has disappeared from the urine. The concentration power is normal 1 month before the filtration rate becomes normal.

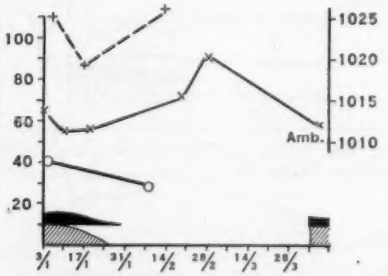
with an *angina phlegmonosa* without symptoms or signs of renal involvement, but a few days after admission albumin and blood

was found in the urine. In this case the albuminuria disappeared first, the erythrocytes disappeared 14 days before the filtration rate became normal. Also it is worth mentioning that the concentration test showed too low values after the disappearance of the albuminuria; but the concentration power became normal 1 month before the filtration rate. Again it is seen that the concentration test is a much coarser test than the filtration test.



CURVE 8.—Intermittent course with relapse of the function to values below normal after disappearance of red blood cells from the urine.

Curve 8 is derived from a boy, aged 4½ years, with scarlet fever nephritis which began on August 10, 1931. The albuminuria disappeared very quickly (August 29) and the microscopic hematuria was very slight. In spite of very careful and repeated examinations erythrocytes were found in the urine, the last time on September 2, but the filtration rate did not become normal until some time



CURVE 9.—Relapse after discharge with normal urine but too low filtration rate. Reappearance of albuminuria and hematuria.

between October 23 and 31. This case further shows that the filtration rate may show rather large variations during the course of the acute nephritis. Improvement and relapses in the function occur in this case, and they are seen not to be concomitant with variations in the sediment.

These 2 cases show the great value of the creatinin test in acute nephritis. It is generally accepted that acute hemorrhagic nephri-

tis can be regarded as cured when albuminuria and microscopic hematuria have definitely stopped. This can no longer be regarded as a safe assumption, when it is beyond doubt that the function may be well below normal at a time when all pathologic findings have disappeared from the urine. That neglect of the still impaired function may cause serious damage to the patient is seen from the following case (Curve 9). The patient, a woman, aged 32 years, entered the hospital on December 7, 1930, with *angina phlegmonosa* with several abscesses. On December 30 acute hemorrhagic nephritis set in. The albuminuria ceased on January 26, 1931, the hematuria on January 31; in 2 later microscopic examinations of the urine nothing abnormal was found. The filtration tended to rise but did not get normal (84 on February 28). On March 1 the patient wanted to leave the hospital. On March 31 she was reexamined, the filtration rate was lower (58) and the urine contained albumin and microscopic blood. Of course, one cannot prove that this relapse would not have occurred if the patient had not been permitted to get out of bed and leave the hospital; but to me it appears very probable that it might have been avoided if the rising tendency of the function, which is shown by the tests on February 21 and 28, had been allowed to continue. It is beyond doubt that the function of the kidney in normal subjects is better in the lying than in the upright position. This has been shown to be correlated with differences in the colloidal osmotic pressure of the plasma in these positions. The bearings of these facts on pathologic conditions have not been investigated, but it is probable that the effect of the position here is still more obvious. One can say that it is desirable to keep the patients with acute nephritis in bed while symptoms of a pathologic state are present, and the facts just referred to may give some understanding as to why the pathologic processes in the kidney are influenced by the patient's lying in bed or getting up.

The case just referred to is a still further example of the concentration test showing normal value when the filtration rate is too low. In these cases I have never seen the creatinin test become normal before the concentration test, and as has already been pointed out the concentration test may be normal several weeks before the filtration rate becomes normal.

It must be pointed out that values marked in the curves as the lower normal level are minimum values for normal persons with a given surface area. The values which patients must reach before I regard their filtration rate as being perfectly normal lie above this minimum value. This is because continued observation has shown that the filtration rate has risen to a higher level. Not until this level has been reached have I considered the filtration rate as normal. This does not affect the conclusion that the microscopic hematuria may disappear several weeks before the filtration rate can be

regarded as normal and that the concentration test may show normal results long before the filtration rate is within the normal zone.

In 3 cases the filtration rate has risen to values much above the average normal level and then fallen a little again. I do not know the significance of this fact. It may be due to a low colloidal osmotic pressure of the plasma, as this tends to enhance the filtration in the glomeruli. These patients were treated with a low protein diet and the protein restriction was lessened when function grew better. The cases were the following:

CASE 1.—A girl, aged 3¾ years, had scarlet fever, about Christmas, 1930, and nephritis, beginning January 5, 1931. Urine still contained albumin and erythrocytes, January 19; no pathologic contents on January 31 and several times later. *Filtration rate:* January 10, 29 cc.; January 15, 23; January 22, 47; January 30, 47; February 6, 34; February 20, 34; *March 7, 66;* March 14, 46; March 20, 46. Her weight was 15.6 kilos. Surface area (Benedict-Talbot), 0.67 sq. m. Minimum filtration rate, 40 cc.

CASE 2.—A girl, aged 3¾ years, the twin sister of Case 1, had scarlet fever and nephritis at the same time as Case 1. Urine still contained albumin and erythrocytes on January 19. On January 31 no albumin, but a few erythrocytes, and again on February 6. On February 13 and several times later no pathologic contents were found. Filtration rate on January 10, 20; January 15, 29; January 22, 45; January 30, 43; February 6, 38; February 20, 28; February 28, 35; *March 7, 60; March 14, 63;* March 20, 56; April 4, 49. Her weight was 15 kilos. Surface area (Benedict-Talbot), 0.657 sq. m. Minimum filtration rate, 40 cc.

CASE 3.—A boy, aged 3 years, had scarlet fever, November 15, 1930, and nephritis, December 4, 1930. The urine on January 19 contained no albumin, but 8 to 10 erythrocytes in each microscopic field; on January 26 a few erythrocytes; on January 31 and several times later no pathologic contents were found. The filtration rate was on December 11, 14 cc.; December 19, 36; December 31, 15; January 8, 21; January 15, 29; January 22, 21; January 30, 30; *February 14, 55;* February 28, 40; March 4, 42. His weight was 14.2 kilos. Surface area (Benedict-Talbot) was 0.62 sq. m. Minimum filtration rate, 33 cc.

Addis and coworkers[8] maintain that the amount of erythrocytes and casts in the urine is a valuable index of the activity of the pathologic process. In these cases no countings of erythrocytes and casts were made. But cases like the 3 quoted in which by several careful examinations no erythrocytes and casts were to be seen, the function being still decidedly below the normal level, to my mind make it doubtful if this quantitative method is absolutely reliable. At any rate it does not seem justifiable to consider the pathologic process as inactive at this stage. The case observed in which relapse occurred speaks strongly against such a standpoint. It is a well-established fact that patients who have gone through an acute nephritis and whose urine had become perfectly normal later on may show all signs of chronic nephritis.

Volhard[2b] writes (page 1303): "The disease can apparently heal and only after a considerable or even lengthy period lead to kidney insufficiency." And quite in accord with this, Siebeck[9] writes:

"There are some patients who after the most careful and expert care are discharged as 'cured' and later, perhaps after years, succumb to a typical contracted kidney." These facts seem to me to make it necessary to treat these patients whenever possible until both chemical and microscopic examinations of the urine and function tests (and the most sensitive tests are desirable) show normal results. Only when this is done can it be said that everything has been done to avoid chronic nephritis as a result of an acute nephritis.

The fact that some follow-up researches often show or appear to show a rather favorable prognosis for acute nephritis does not alter the desirability of being as certain as possible of the acute nephritis being cured when treatment is stopped. Hansborg[10] has reëxamined patients with scarlet fever nephritis and shown that relapses and cases that had become chronic could not be found. On the other hand, reëxaminations of cases of war nephritis both from English and German authors (Hume and Nattras,[11] Gros[12]) show that at least one-third of the cases become chronic, while only about half of all cases have completely recovered. Tallermann[13] has examined 27 cases of acute nephritis in children; of these 2 died and 18 are regarded as recovered, 4 show evidence of renal damage. As most of his patients were discharged when the urine still contained red blood corpuscles and albumin this might be considered as an evidence that rigorous treatment until normal urine and normal function is reached is not necessary. But, still, 4 patients with renal damage out of 25 patients discharged is not quite a small number; and further, 8 patients could not be considered as "completely recovered," 2 being considered as "probably completely recovered" and 6 as "recovered." Of these 8 patients 7 had albuminuria on reëxamination, 1 had only a slightly impaired phenolsulphonephthalein excretion but no albuminuria. As the function tests used in these examinations (blood urea, urea concentration and phenolsulphonephthalein) are very coarse tests, marked renal damage cannot be excluded in these cases. In other words, only 13 patients out of 25 can safely be regarded as being cured. Tallermann's material seems to me to speak strongly for the necessity for the rigorous treatment of patients with acute nephritis.

The ideal result to attain is that the patient has no albuminuria, that the centrifugate from the urine does not contain abnormal elements and that the function as judged by the creatinin test and the concentration test is normal. That we sometimes cannot reach this ideal is obvious. In such cases where albumin and erythrocytes do not completely disappear it seems to me that the finding of a normal filtration rate permits a favorable prognosis and to some degree speaks in favor of the diagnosis "Restalbuminurie" and against chronic nephritis.

Is a *topical diagnosis* by means of the creatinin test possible?

It is well known that the concentration power may be maintained in acute nephritis. I have shown several cases in which the concentration power is regained before the filtration rate as determined by the creatinin test becomes normal. The case illustrated in Fig. 9 is a good example of the fact that the concentration power at the onset of the acute nephritis may be normal while the filtration rate is markedly impaired. I will give some further examples:

CASE 4.—Poul H., aged 5 years, had scarlet fever, September 29, and nephritis, October 15. On October 15 the 24-hour urine had a specific gravity of 1021; on October 16 the filtration rate was 16 cc. per minute; on October 17 the 24-hour urine had a specific gravity of 1019. His filtration rate rather quickly went up again, on October 29 it was 45 cc.; his normal value was about 55 cc.

CASE 5.—Poul B., aged 10 years, had scarlet fever on September 15 and nephritis on October 5. October 7, specific gravity, 1025. October 8, filtration rate 25 cc., specific gravity 1021. October 9, specific gravity 1020. His normal value for the filtration rate was about 80 cc.

It should be emphasized that none of these urines contained so much albumin that it could affect the specific gravity.

I have not seen the concentration power maintained in cases in which the filtration rate was very seriously impaired (below 10 cc. per minute).

Volhard explains the fact that the concentration power may be maintained in acute nephritis according to his theory. He says that the tubuli are able to excrete solids to a normal extent while the capsules on account of ischemia cannot excrete water. The low creatinin clearance combined with maintained concentration power must mean either that creatinin is excreted through the capsules—and this is not in accord with the views of Volhard—or that the power of the tubules to excrete creatinin alone and not other solids is impaired, which is absurd. It is difficult to explain this discrepancy between the creatinin clearance and the concentration power in any other way than by assuming that the creatinin is filtered through the capsules. If the filtration rate is very seriously impaired or if it has been damaged for a long time it is no wonder that the concentration power is found lowered. That is on account of the anatomical facts. The tubules may atrophy from inactivity, and further it must be kept in mind that by far the largest amount of blood which goes to the tubules passes the glomeruli. When the arteries do not let the blood pass on account of either functional ischemia or ischemia from obturation of the capillaries, the blood supply of the tubules must suffer and so also the function of the tubules. Hence the lowered creatinin clearance must mean lowered filtration rate in the capsules—a suffering of the capsules—the lowered concentration power that the tubules are suffering. When the concentration power is maintained while the filtration rate is normal this means that the capsules are seriously involved by the morbid

process while the tubules are free or relatively free. Thus in acute nephritis a topical diagnosis by function tests is possible to a certain extent. In chronic nephritis this possibility does not exist because both the capsule and the tubule—the whole "nephron"—are and must be suffering.

Is it possible to draw any prognostic conclusions from the degree of the functional impairment? It is evident from my material that even when this has been very large the restoration may be complete (see for instance the case illustrated in Curve 4 in which the filtration rate was only 10 per cent, and the case illustrated in Curve 5 in which it was only about 8 per cent of the normal value.) But if the 2 cases which became chronic (Curves 1 and 2) are analyzed it will be seen that both of them show a very marked functional impairment and this very severe damage lasts for a long time. In the case illustrated in Curve 1 the filtration rate 8 weeks after the onset is still about 30 cc. per minute, *i. e.*, only 30 per cent of the normal value; not until 9 to 10 weeks after the onset a marked rise occurs. In the other case also more than 2 months elapsed after the onset of the nephritis before a marked rise of the filtration rate set in; 9 weeks after the onset the filtration rate is only 30 per cent of the normal.

This very long duration of the serious functional impairment has not been seen in the other cases. Compare, for instance, the case from Curve 5, just quoted, in which the damage was severe. Here the filtration rate 3 weeks after the onset has already risen to more than 50 per cent of the normal. And in the case from Curve 4, also with a very severe damage (down to 10 per cent) the rise is still sharper so that the filtration rate only 10 days after the onset has risen to about 85 per cent of the normal. In other cases the rise is less sharp but then the damage will be seen to have been less serious.

My impression is that when the functional impairment is large and does not recede within 4 to 6 weeks, this means that the danger of the nephritis becoming chronic is very menacing. If the filtration rate reaches values of about 50 per cent within 4 weeks the prognosis seems to be good, even if the filtration rate at the beginning has been very low.

As it will be readily seen from the curves, the blood urea rapidly falls when the patients get under treatment. Of course, the raised blood urea means that the kidney function is much impaired, but as it may be normal at a time when the function is still very far from being normal it is not of any value at the time when improvement is going on and it is to be determined if the function has got normal. The value of the blood urea determination as a kidney function test has been spoken of in a former paper to which the reader is referred.[4]

The blood pressure is not—at any rate not directly—dependent on the kidney function. Nevertheless it has been used as a guide

for treatment. Volhard considers it unnecessary to keep the patient in bed when the blood pressure has fallen to normal. As it will be understood, I cannot agree with this standpoint. The blood pressure has in all these cases fallen to normal long time before the function has got normal. It cannot be denied that the impaired function must be a less coarse sign of the morbid process in the kidneys than the blood pressure rise. This may be influenced by several extrarenal factors and further it is by no means known to be produced by the morbid process in the kidney.

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THE KETOGENIC DIET IN NORMAL INDIVIDUALS: A BIOCHEMICAL INVESTIGATION.

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During the last 10 years a number of reports have appeared on the good results of treatment of epilepsy and asthma by the ketogenic diet, especially in American journals, by Wilder,[12] Peterman,[5] Talbot, Metcalf and Moriarty,[7] Lennox and Cobb,[4] Helmholtz[2] and others.

Nobody, however, so far as we are aware, has made a complete examination of the changes in the acid-base balance of the blood under the influence of this diet, though Weymuller and Schloss[11]

reported the results of some partial examinations of the blood of normal and asthmatic children.

The Ketogenic Diet. Wilder,[12] of the Mayo Clinic, noted that certain epileptic patients improved with starvation and the consequent acetonuria, and he suggested the possibility of the use of high fat diets in the treatment of epilepsy, a method which has been steadily developed, until now it is generally accepted as one of the best of the known methods of treatment. The well-known effect of acidosis in producing a relaxation of smooth muscle would also suggest its use in such conditions as asthma.

Briefly the method consists in increasing the $\frac{\text{fatty acid}}{\text{dextrose}}$ $\left(\text{or}\ \frac{\text{ketogenic}}{\text{antiketogenic}}\right)$ ratio in the diet. The value of this ratio is calculated from the formula $\frac{0.44P + 0.9F}{C + 0.56P + 0.1F}$ since proteins, and to a small extent fats, contain ketogenic and antiketogenic substances. In ordinary diets the value of the fatty acid-dextrose ratio is about 1 to 2. With patients this ratio is gradually increased to 1 to 1, 2 to 1 and, finally, 3 to 1 or even more. Ketone bodies appear in the urine within the first 2 or 3 days, and improvement is often noted within the first week. Many cases, however, appear to be refractory to treatment, and in asthma, at any rate, adults are not so favorably affected as children. It occurred to us that a complete examination of the blood as regards acid-base changes might throw some light on this problem, since variations in the acid-base balance, though probably not the cause of epilepsy and asthma, accompany and experimentally influence these diseases.

Methods. Three healthy women students, aged from 21 to 23, volunteered to undergo the examination. For 18 days they adhered rigidly to the ketogenic diet, under the direction of Miss Mabel Flanley, B.S., Consulting Dietitian, of Seattle, Washington. Blood examinations were made in each before commencing the diet, on the 9th and 18th days and again 18 days after return to normal diet, thus making 4 blood examinations in all.

From the fasting subject, at 9 A.M., 30 cc. of blood were drawn without stasis from the median basilic vein into a large Record syringe containing a standard amount of potassium oxalate as anticoagulant. The whole blood was then "arterialized" by bringing it into equilibrium with alveolar air, using the method described by van Slyke.[8] A portion was next transferred under oil, without loss of CO_2, to a centrifuge tube, centrifuged for $1\frac{1}{2}$ hours, and the plasma separated. The following were then determined:

(*a*) The chlorid content of both whole blood and plasma (method of van Slyke[9]).

(*b*) The carbon dioxid combining power of both whole blood and plasma (van Slyke[8]).

(*c*) The relative volumes of corpuscles and plasma in the whole blood (hematocrit method).

From the above a simple calculation gave us:

(*d*) The chlorid content per 100 cc. of red cells.

(*e*) The carbon dioxid combining capacity per 100 cc. red cells.

All estimations were made in duplicate, and the figures for red cell volumes per cent are each the average of 4 determinations. We are, of course, aware of the difficulties in determining the true red cell volume per cent by any hematocrit method, as has been well shown by Ponder and Saslow.[6] As their method requires 35 cc. of blood in addition to that required for chlorid and carbon dioxid concentrations, it was obviously undesirable to use their method with our young female subjects. Since, however, we were concerned with showing comparative changes in the blood of each subject at various times, and we used the same method for all (1600 revolutions per minute for 1½ hours in uniform bore hematocrit tubes), we feel, as Ponder and Saslow themselves state, that the hematocrit method may be useful for the determination of relative changes in cell volume. That this method as employed by us may give good comparative results is shown by the straightness of the curves in Fig. 4.

TABLE 1.—MISS B.

Date.	Carbohydrate.	Protein.	Fat.	Calories.	F.A.:G. ratio.	Urine tests.				Wt.	Remarks.
						Rothera.		Lange.			
						A.M.	P.M.	A.M.	P.M.		
June											
16	75	45	195	2215	1.7:1	....	....	....	....	144	Blood exam.
17	75	45	195	2215	1.7:1	+++	....	....	....	143½	
18	75	45	195	2215	1.7:1	++	++	....	....	143½	Very heavy and sleepy.
19	75	45	195	2215	1.7:1	++	++++	....	....	143½	Very heavy and sleepy.
20	42	45	195	2083	2.1:1	++++	+++	++	++	142½	Very heavy and sleepy.
21	42	45	195	2083	2.1:1	....	....	+++	++	..	Headache.
22	32	45	214	2324	2.7:1	....	....	+	++	141	
23	32	45	214	2324	2.7:1	....	....	++	+	141	
24	32	45	214	2324	2.7:1	....	....	+++	++	140½	Blood exam.
25	32	45	214	2324	2.7:1	....	....	+++	+	140½	Easily tired.
26	23	48	230	2300	3.0:1	....	....	+++	+++	140½	
27	23	48	230	2300	3.0:1	....	....	++++	+++	140	
28	23	48	230	2300	3.0:1	....	....	++++	+++	..	
29	23	48	230	2300	3.0:1	....	....	++++	+++	139½	Nausea.
30	23	48	230	2300	3.0:1	....	....	++++	+++	139½	
July											
1	37	48	230	2500	2.7:1	....	....	+++	+++	139	Headache, nausea at night.
2	37	48	230	2500	2.7:1	....	....	+++	++	139	More normal.
3	37	48	240	2500	2.7:1	....	....	+++	++	139	More normal.
4	..	..	..	...	...	....	....	....	....	...	Blood exam.

Results and Their Significance. Tables 1, 2 and 3 show details of the diets used, together with urinary tests, and Figs. 1, 2 and 3 show the changes that took place in the blood during the period of examination as regards the concentrations of chlorids and bicarbonate in both plasma and red cells. Unfortunately no observations of urinary pH were made. In all subjects the following blood changes were found: (*a*) A slight fall of plasma carbon dioxid; (*b*) a more marked fall of red cell carbon dioxid; (*c*) a fall in the

ratios $\frac{(CO_2)\ c}{(CO_2)\ p}$ and $\frac{(Cl)\ c}{(Cl)\ p}$ (there is 1 exception to this, Fig. 1); (*d*) a fall in the total volume of the red cells.

TABLE 2.—MISS M.

Date.	Carbohydrate.	Protein.	Fat.	Calories.	F.A.:G. ratio.	Urine tests. Rothera. A.M.	Rothera. P.M.	Lange. A.M.	Lange. P.M.	Wt.	Remarks.
June											
15	78	41	196	2240	1.70:1	....	++	....	....	123	Blood exam.; very tired.
16	78	41	196	2240	1.70:1	++	....	....	....	122	Very hungry.
17	78	41	196	2240	1.70:1	+	++	....	....	122	Nausea before breakfast; hungry.
18	78	41	196	2240	1.70:1	+++	+++	....	....	121½	Meals difficult to dispose of, especially butter.
19	78	41	196	2240	1.70:1	+++	+++	+++	++	121½	Normal all day.
20	81.9	41	210.6	2390	1.60:1	++++	+++	+++	++	121½	Very tired; nausea; afternoon in bed.
21	81.9	41	210.6	2390	1.60:1	....	....	+++	++	121½	Headache all day.
22	46.8	41	210.6	2246.6	2.20:1	....	....	++	+++	121	
23	46.8	41	210.6	2246.6	2.20:1	....	....	+++	++	120½	
24	46.8	41	210.6	2246.6	2.20:1	....	....	+++	++	120½	Blood test.
25	46.8	41	210.6	2246.6	2.20:1	....	....	+++	+++	120	
26	33.69	41	224.6	2320	2.75:1	....	....	+++	++	119	Normal.
27	33.69	41	224.6	2320	2.75:1	....	....	+++	+++	119	Giddiness.
28	33.69	41	224.6	2320	2.75:1	....	....	+++	+++	..	Tire easily since on diet; poor sleep.
29	33.69	41	224.6	2320	2.75:1	....	....	+++	+++	118½	Hungry all day.
30	38.55	41	228.6	2631	2.60:1	....	....	+++	+++	119	Nausea before breakfast.
July											
1	38.55	41	228.6	2631	2.60:1	....	....	+++	+++	119	Normal.
2	38.55	41	228.6	2631	2.60:1	....	....	+++	+++	119	
3	..	..	..	...	...	....	....	+++	....	..	Blood exam.

TABLE 3.—MISS T.

Date.	Carbohydrate.	Protein.	Fat.	Calories.	F.A.:G. ratio.	Urine tests. Rothera. A.M.	Rothera. P.M.	Lange. A.M.	Lange. P.M.	Wt.	Remarks.
June											
15	95	42	243	2735	1.60:1	+	−	....	....	110	Blood exam.
16	95	42	243	2735	1.60:1	+++	+	+	−	109	Depression.
17	95	42	243	2735	1.60:1	++	+	−	=	110	Sleepy and listless.
18	95	42	243	2735	1.60:1	++	++	+	+	109½	
19	95	42	243	2735	1.60:1	....	....	++	++	110	Very tired.
20	54	42	243	2571	2.20:1	....	....	++	++	109½	More normal.
21	54	42	243	2571	2.20:1	....	....	++	++	..	Normal.
22	54	42	243	2571	2.20:1	....	....	++	+++	108	Nausea.
23	40	42	258	2700	2.77:1	....	....	++	++	107	Nausea and faintness.
24	40	42	258	2700	2.77:1	....	....	++	++	107½	Blood exam.
25	40	42	258	2700	2.77:1	....	....	+++	++	107½	Listless.
26	33	42	270	2700	3.10:1	....	....	+++	++	107	Tired.
27	33	42	270	2730	3.10:1	....	....	++	+++	107	Normal.
28	33	42	270	2730	3.10:1	....	....	+++	+++	..	Normal, day; nausea, night.
29	33	42	270	2730	3.10:1	....	....	+++	+++	106	
30	33	42	270	2730	3.10:1	....	....	+++	+++	106½	
July											
1	33	42	270	2730	3.10:1	....	....	+++	+++	107	
2	33	42	270	2730	3.10:1	....	....	+++	?	108	
3	..	..	..	...	...	....	....	+++	....	..	Blood exam.

In order to interpret these results we have applied the laws relating to the distribution of chlorid, bicarbonate and hydrogen

ions in blood, which have been worked out, during the last few years, by van Slyke and his fellow workers.[10]

According to one of these laws, the ratio of chlorid concentration in cells to chlorid concentration in plasma is equal to the ratio of

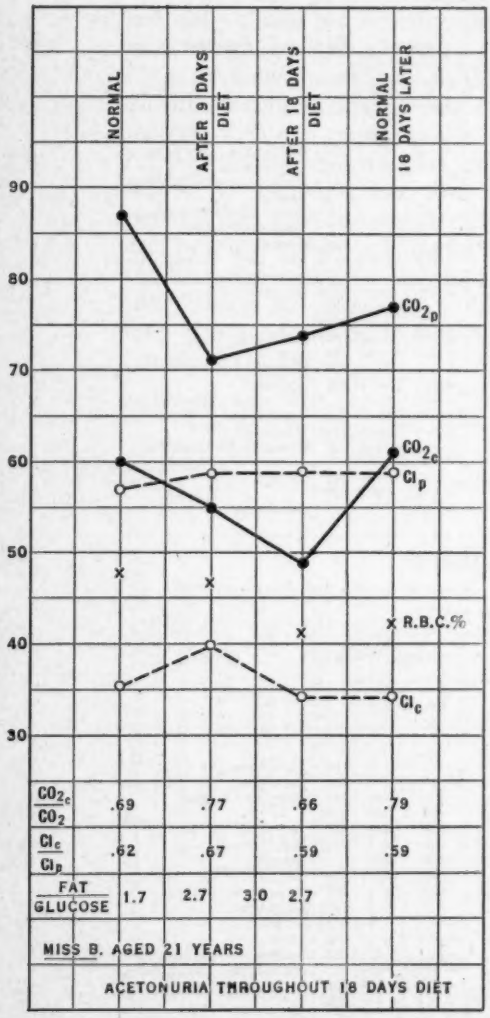

FIG. 1

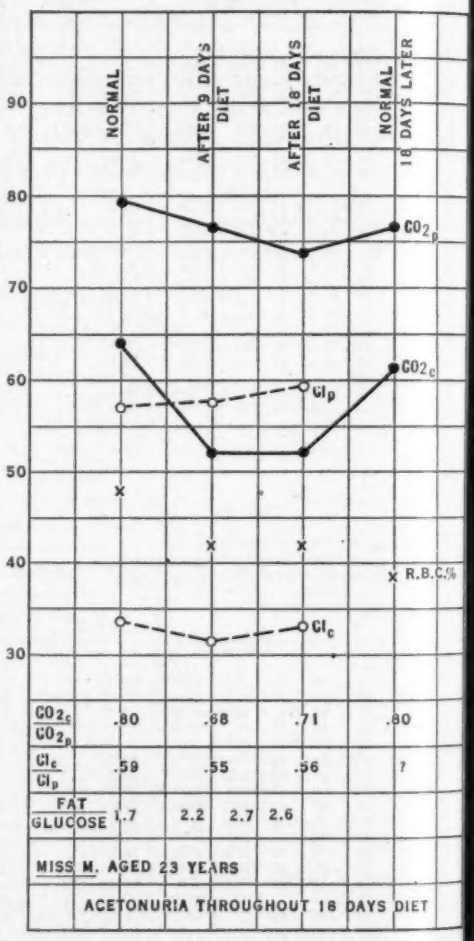

FIG. 2

bicarbonate concentration in cells to bicarbonate concentration in plasma. The numerical value of this ratio is determined by the concentration of base-binding hemoglobin in the red cells, which in turn depends on the hydrogen-ion concentration of blood. Further,

the value of the ratio rises with increase of hydrogen-ion concentration, or acidemia, and falls in alkalemia. These laws may be expressed thus:

$$\frac{(Cl')c}{(Cl')p} = \frac{(HCO_3')c}{(HCO_3')p} = \frac{(H^+)p}{(H^+)c} = 1 - \frac{(Hb')c}{2(Cl' + HCO_3')p}$$

(The use of the parenthesis is to indicate concentration of ions.)

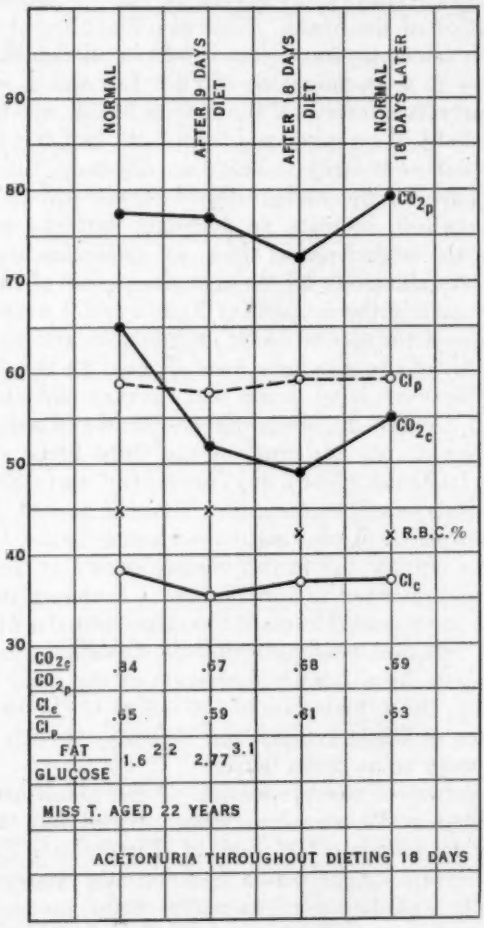

FIG. 3

FIGS. 1, 2 and 3.—Abscissæ represent c.gm. NaCl and cc. of CO_2 per 100 cc. of plasma or red cells.

In actual practice this law, though not absolutely true, is near enough for our purposes. Its mechanism is well illustrated by one of our experiments (Fig. 4), in which the hydrogen-ion concentration

of a sample of blood has been raised by the addition of hydrochloric acid. It will be noted that the curves representing carbon dioxid combining power (bicarbonate) of both plasma and cells not only fall but converge as more acid is added. The plasma and cell chlorid curves also converge. Convergence of curves means that the ratios $\frac{(Cl')c}{(Cl')p}$ and $\frac{(HCO_3')c}{(HCO_3')p}$ rise in value as the blood becomes more acid. Conversely a divergence of curves indicates a more alkalin condition of the blood. Note also that the red cell volume also rises with acidemia; conversely it falls in alkalemia.

Coming now to a consideration of Figs. 1, 2 and 3, we find that in all the bicarbonate reserve of the plasma fell, as was found in the case of children by Weymuller and Schloss.[11] But this fall in alkali reserve does not necessarily indicate an acidemia. In Fig. 1 the early convergence of the carbon dioxid curves and of the chlorid curves does, indeed, indicate an acidemia, but the even greater divergence in the second period shows an alkalemia, and in Figs. 2 and 3 there was alkalemia all through the period of the ketogenic diet. Unfortunately the subjects of Figs. 2 and 3 were menstruating at the time of the second blood examination and we are unable to state how far our results have been affected by this fact. Close and Osman,[1] however, have shown that the only effect of menstruation is a slight decrease in plasma carbon dioxid and a slight increase in plasma chlorid. At the time of the third blood examination menstruation had ceased 8 or 9 days previously, and still a condition of relative alkalemia was present. The fall in red cell volume throughout the period of examination can hardly be due to alkalemia, since the most marked fall in cell volume occurs at the end, when the subjects had returned to normal diets. A more plausible explanation is that the repeated losses of blood has caused a slight anemia.

Discussion. In this wholly unexpected alkalemia—accompanied, as is well known, by a further hydration of the body tissues—we have, probably, the explanation of the failure of the ketogenic diet in many cases of adult asthma and epilepsy, though in children the results appear to be much better.

The explanation of the production of the alkalemia is a more difficult problem. We would, however, tentatively suggest that the clue may be found in the work of Hurtley and Trevan,[3] who showed that certain ketone derivatives not only produce coma, but also specifically stimulate the respiratory center, producing hyperpnea and increased rate of respiration. This action is due to the unsaturated linkage in the group —C.OH=CH— found in these substances, and occurs when the substances are neutral bodies or have been neutralized, so that the effect is not due to an alteration of hydrogen-ion concentration.

The ketonic acids, of course, tend to produce acidemia by combining with the sodium bicarbonate of the blood and raising the

$\frac{(HCO_3)c}{(HCO_3)p}$ ratio, in the same way as does hydrochloric acid in Fig. 4. But the hyperpnea produced by direct stimulation of the respiratory center by the —C.OH=CH— bodies causes carbon dioxid to be blown off in excess by the lungs, leaving a relative excess of uncom-

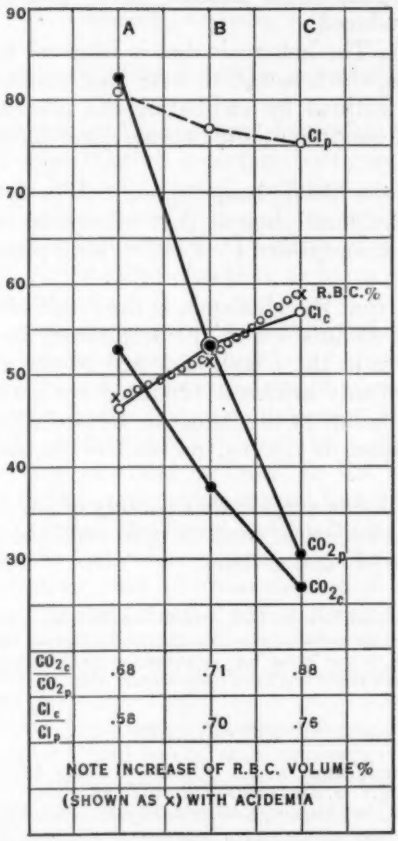

FIG. 4.—Graph illustrating the redistribution of Cl and CO_2 between plasma and red cells when the H content, but not the Cl content, is altered in blood *in vitro*.
In A, 40 cc. of blood + 1.5 cc. 0.5 N NaCl solution.
In B, 40 cc. of blood + 0.75 cc. 0.5 N NaCl solution.
+ 0.75 cc. 0.5 N HCl solution.
In C, 40 cc. of blood + 1.5 cc. 0.5 N HCl solution.
Abscissæ represent c.gm. NaCl and cc. of CO_2 per 100 cc. of plasma or red cells.

pensated bicarbonate in the blood, *i. e.*, an alkalemia. Of course, the kidney tends to restore the $\frac{H_2CO_3}{NaHCO_3}$ ratio in the blood by excreting the excess $NaHCO_3$, but as these compensating mechanisms never quite succeed in restoring the ratio to normal (since if they did so

the stimulus to compensate would disappear) the result is that a slight alkalemia remains.

We have then two effects, one tending towards an acidemia, the other tending in the reverse direction. The final result would appear to depend upon which of these preponderates, or the relative proportions in which ketonic acids and —C.OH=CH— groupings are produced.

Conclusions. 1. The ketogenic diet is believed by many to produce an acidemia which is said to have good results in many cases of epilepsy and asthma by combating the alkalemia often associated with these conditions, and causing some dehydration of body tissues.

2. A study of the blood changes produced by the ketogenic diet in 3 normal individuals showed that alkalemia was almost constantly present, accompanied by a fall in both plasma and red cell carbon dioxid.

3. We suggest that the alkalemia is the result of hyperpnea produced by direct stimulation of the respiratory center by certain ketone derivatives in the blood, and that in our experiments this effect outweighed any acidemia produced by ketonic acids, and, further, that the failure of the ketogenic treatment of many cases of epilepsy and asthma is due to the relative preponderance of the former effect.

4. We would further suggest that a study of any conditions tending to raise the ketonic acid:acetone ratio would be of benefit in the treatment of epilepsy and asthma.

NOTE.—To Miss Mabel Flanley, B. S., consulting dietitian of Seattle, Washington, are due our thanks for her great help in arranging and directing the dietetic treatment of our subjects, and to the latter for volunteering their services. Without their valuable help this work could not have been carried out.

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THE COLON CHANGES IN CHRONIC ARTHRITIS COMPARED WITH OTHER CHRONIC DISEASES.*

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Recently the concept has been put forth that in chronic arthritides the bowel may take on a certain configuration, such as redundancy, atony, lack of haustral markings and ileocecal valve incompetency (Pemberton and Peirce,[1] Fletcher and Graham[2]). In addition, Pemberton has stressed the effect of a low calorie diet, with a minimum carbohydrate fraction, as being particularly beneficial to arthritic patients.

Having had occasion to study a number of arthritics in this dispensary from various angles, we aim here to compare the appearance of the bowel in chronic arthritis and in a group of dispensary patients with various other chronic ailments. This should determine whether the changes were characteristic of chronic arthritis or were merely such as would be found in the bowels of chronic patients subject to the same environmental factors.

Everyone admits that the bowel has changed through the ages in conformity to the type of diet ingested. If it were possible to compare the digestive tract of Pithecanthropus Erectus with the digestive tract of the individual of today changes would doubtless be noted. The preponderance of vegetables and fruit, with an excess of roughage eaten for hundreds of thousands of years before the cooking era, certainly made the digestive tract of that era somewhat different from ours. These changes are in a measure comparable to those found in the skull and other osseous development of the ape man of Java, compared with the human skeleton today. In addition to these adaptions of the alimentary tract in response to food and environment, changes in the bowel developed —"as a result, either of congenital anomaly of the colon or of an instability of its autonomic control or from an interplay of both factors" (Kantor[3]).

The bowel has an intimate relationship both to disease and health. Here is one of the main sources of elimination of the waste products of digestion. Any breakdown in the metabolism of the individual, any impairment in the function of the liver as a detoxifying agent, any curtailment of the excretory power of the genito-urinary tract, any change in the secretion of the digestive enzymes of the stomach

* This investigation was pursued with kind permission of Dr. E. C. Reifenstein, Professor of Medicine and Chief of Service.

and upper intestinal tract; the adoption of dietetic fads and fancies, or the inadequate diets now eaten by a large majority of dispensary patients because of economic reasons, show their effect in one way or another on the large bowel. To this number, as a result of our studies detailed below, we must add a group of patients who, like the chronic arthritics, have certain characteristic changes in their bowel. We maintain that this is not typical or peculiarly characteristic of these special diseases, but is more or less a manifestation of chronic ill-health, malnutrition and inadequate diet in general.

Bouchard[4] and Metchnikoff[5] stress the importance of intestinal toxemia to disease in general and the prevention of bowel stasis in prolonging life. Lane[6] and Goldthwait have called our attention to anatomic changes in the intestinal tract, such as bands, kinks and visceroptosis and their effect on intestinal stasis with its resultant toxemia and general ill-health.

All kinds of operations have been suggested to correct the malposition of the colon, the removal of kinks, the resection of parts of the bowel in cases of redundancies. Ileocecal valve incompetencies have also been subjected to operative interference. All these measures have been attended with varying indifferent results.

Pemberton and Fletcher have claimed that in their particular studies, with the improvement in the general arthritic condition, redundancies of the bowel have been lessened, ileocecal valve incompetencies were reduced to a minimum, atony improved and haustral markings were made to appear again where once they were lacking.

In our study we observed very carefully roentgenologically, by means of barium enemas, 25 chronic arthritic cases and 25 cases representative of the average run of dispensary patients coming to the clinic for consultation.

The Roentgen appearance of the bowels of the arthritic patients showed an unusual percentage of redundancies, lack of haustral markings, atonies and ileocecal valve incompetencies. In this respect our results were comparable in every way, with the studies previously made by Pemberton and Fletcher.

We found in our studies that 80 per cent of our arthritic patients showed ileocecal valve incompetency of varying degrees. There was lack of haustral markings exhibited in 64 per cent of our cases. For the most part, these markings were observed in the descending colon. In 40 per cent of our cases atony was exhibited. We found the rather high proportion of redundancies of parts of the colon in 85 per cent of our cases. These redundancies took on various forms, such as pleats, loops and knots.

In the same type of investigation made of our control group we found reduplications in 80 per cent; lack of haustral markings in 78 per cent; ileocecal valve incompetencies in only 16 per cent; atony of the bowel in 8 per cent. It will be seen that the chief point of difference between the two groups is in the higher incidence

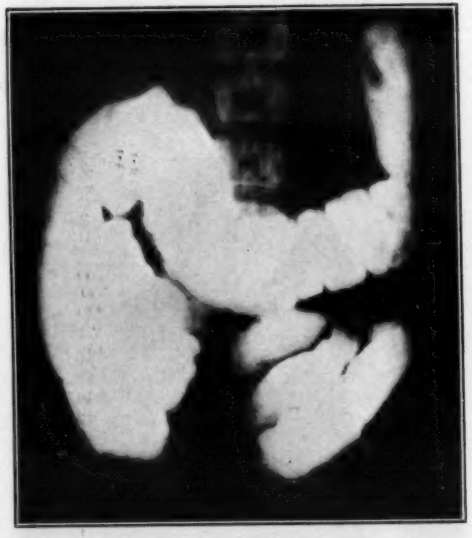

FIG. 1.—Mrs. V. H. Psychoneurosis, anxiety state. Redundancy.

FIG. 2.—Mr. N. H. Chronic arthritis. Redundancy.

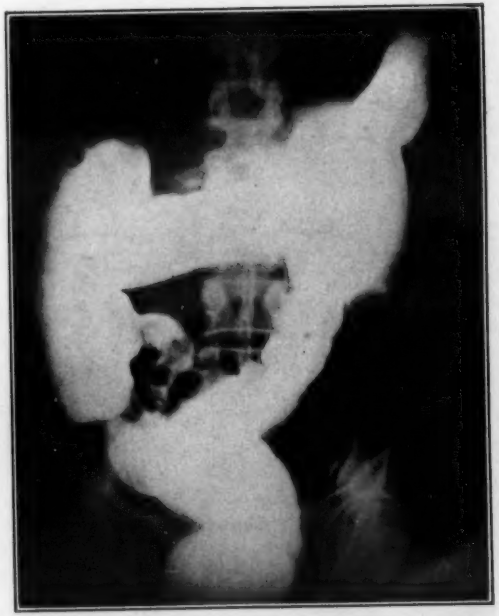

FIG. 3.—Mr. P. R. Chronic arthritis. Ileocecal valve incompetency.

FIG. 4.—Mrs. H. D. Psychoneurosis, anxiety state, metrorrhagia. Lack of haustral markings. Redundancy.

FIG. 5.—Mrs. A. M. Pulmonary tuberculosis (arrested); rheumatic heart disease; ptosis and redundancy.

FIG. 6.—Mr. E. F. Chronic arthritis. Ptosis and redundancy.

of ileocecal valve incompetencies exhibited in the chronic arthritides. The etiologic significance of this finding in relationship to arthritis will not be discussed in this paper.

Redundant Colon. A redundant colon is one of the most commonly seen departures from the normal colon. The ideal colon would supposedly take almost a straight path in each of its divisions from the cecum to the rectum. The redundant colon, as its name suggests, has its length much increased by kinks, pleats, twists or loops. The normal incidence of redundancies found by Curschmann[7] was 6 per cent; Kantor[8] found an incidence of 9.2 per cent; in a later series he changed this percentage to 19 per cent; Bryant,[9] working with postmortems, found 14 per cent of redundancies of the colon.

The redundancies of the colon most often occur in the pelvis. The normal colon is about 1.5 m. in length. The average colon is able to hold a little over 1 quart of fluid whereas the redundant colon is able to retain much more than that amount, even up to 3 quarts. The significance of redundancy of the colon is a matter of conjecture. It is fair to presume that there must be a large number of patients who have redundancy with absolutely no symptoms, just as it is in the case of a large number of asthenic individuals with ptosis who complain of no symptoms. They probably are more prone to volvulus and constipation than are people with normal colons.

Examples of redundancies can be seen in Figs. 1 and 2.

Ileocecal Valve Incompetency. The ileocecal valve is formed by the invagination of the ileum into the cecum. It has a definite sphincter control, formed by the circular muscle fibers; the longitudinal muscle fibers have been lost. The efficacy of the valve is obtained in the oblique manner in which the ileum enters the cecum, almost in the same manner as the ureter enters the bladder.

The competency of this valve has been a question which has engaged the attention of investigators for a great number of years. The significance of incompetency is still debatable. It certainly is met with in normal individuals in a small percentage of cases and any pathologic significance attributed to this isolated phenomenon alone is speculative rather than based upon scientific corroboration. Keith,[10] Hurst,[11] Case,[12] Stierlin[13] and Jones[14] are only a few of the men who have given this matter serious attention. It was Cole[15] who first recorded this phenomenon roentgenologically in 1902 and since then it is seen rather commonly in Roentgen ray studies of the bowel with contrast material.

Fig. 3 is an example of ileocecal valve incompetency. Figs. 1 and 2 show a competent ileocecal valve.

Lack of Haustral Markings. Normally, there are 3 haustra in the colon; the upper, the middle and the inferior haustrum. Of these, it is only possible to see 2. The third haustrum is hidden by the central axis of the colon. Haustration is caused by the

circular fibers which, acting with a tænia, produce the usual picture of haustration as seen in the roentgenograph. In certain conditions, as in mucous colitis, there may be loss of these haustrations which varies from a small degree to complete absence. In certain extreme cases there are only very small indentations in the lumen of the bowel. This is also seen in the group of chronic cases studied above, without any evidence of colitis.

Fig. 4 shows lack of haustral markings, together with marked redundancy of the left bowel.

Ptosis. Ptosis or coloptosis means dropping of the colon, and may be either congenital or acquired. Asthenic individuals are more apt to acquire it than any other type. It is found much more frequently in women than in men and about 20 per cent of all women have it. Any chronic wasting disease with resulting malnutrition may cause a loss of power of the supporting structures of the intestines and so produce ptosis. However, it most intimately concerns itself with loss of muscle tone in asthenic, congenital, constitutional states. Ptosis of the bowel further depends to a considerable degree on the amount of space in the abdominal cavity, the position of the diaphragm and the liver and the amount of fat deposited in the roots of the mesentery of the intestines.

When the drainage of the colon is retarded in cases of coloptosis symptoms may arise as a result of fermentation and putrefaction of its contents, but in most cases it is fair to state that no symptoms referable to ptosis of the bowel exist. The majority of such patients have no symptoms referable to this condition unless complicated by other factors.

Examples of ptosis are illustrated in Figs. 5 and 6.

It is our opinion that any isolated one of these variations described above may be seen in individuals without causing any particular symptoms, but they may assume a real significance when associated with a chronic wasting disease or may be an expression of chronic disability itself.

We believe that a study of any large group of chronically ill patients would disclose similar variations in the bowel from the normal. With improvement in the general wellbeing of these patients, due to a better dietary régime, more ideal living conditions and freedom from the stress and strain of economic requirements, a more normal bowel would be seen.

Summary. A study of the bowel of 25 chronic arthritic cases shows a high percentage of ileocecal valve incompetencies, reduplications, lack of haustral markings and atonies.

A similar bowel study of 25 dispensary patients with nonarthritic chronic ailments reveals also a high incidence of the above variations.

There is a greater percentage of ileocecal valve incompetency in the arthritics than in the controls, the significance of which we do not attempt to explain at this time.

It is suggested that the expression of the abnormalities in the bowels of the arthritics, as well as in the control cases, is a manifestation of chronic diseased states rather than a condition which is peculiar to the chronic arthritides.

NOTE.—The material for this study was furnished and collected by Dr. Albert A. Bailey, resident physician, Syracuse Free Dispensary.

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INSULIN RESISTANCE DUE TO ALLERGY.

WITH REPORT OF A CASE.*

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ALLERGIC phenomena occurring in cases in which insulin is used are manifested in a variety of ways, as was shown in a review of insulin allergy recently published.[2] The majority of allergic reactions are characterized by local irritation at the site of injection, which is of no serious consequence and merely causes annoyance. Sometimes there is a severe local reaction which causes intense distress, so that further treatment may become difficult. Rarely

* Submitted for publication October 5, 1932.

there is a generalized anaphylactic reaction in which occur urticaria, nausea, vomiting and occasionally circulatory collapse.

The incidence of allergic reactions to insulin is variable. In cases treated at The Mayo Clinic in 1930 and in the early part of 1931 there was some sort of reaction in 1 of every 7 or 8 cases. The number of reactions encountered previously was smaller and the number has also declined recently. In Table 1 are shown the data previously reported, with later figures added. The cause of these changes cannot be explained satisfactorily. Reactions occur from insulin obtained from every source. They occur from insulin made by every manufacturer and from extracts of pancreas of various species. There are, however, differences in the number of reactions encountered with different lots of insulin. One must, therefore, suspect that variability in these reactions may be due partly, at least, to differences in the quality of the preparation. They may perhaps become less common as a result of the efforts which are being made constantly by the manufacturers to improve their methods of extraction and purification. It cannot be expected, however, that allergic phenomena will disappear entirely, for certain subjects show hypersensitiveness to insulin of absolute purity which has been prepared in crystalline form.

TABLE 1.—INCIDENCE OF ALLERGIC REACTIONS.

Date.	Patients treated.	Reactions.	Per cent.
1927—First 6 months	192	7	3.9
Second 6 months	236	7	2.9
1928—First 6 months	168	6	3.5
Second 6 months	211	11	5.2
1929—First 6 months	183	12	6.5
Second 6 months	177	17	9.6
1930—First 6 months	216	34	15.7
Second 6 months	185	23	12.4
1931—First 6 months	206	29	14.1
Second 6 months	202	19	9.3
1932—First 6 months	132	9	6.8

In the majority of cases desensitization occurs spontaneously as the treatment with insulin is continued, and if the irritation is slight it may give no concern. In fact, the patient often fails to bring it to the notice of the physician. Yet attention to these cases, which are so often overlooked, may give gratifying relief. When there is a severe inflammatory reaction at the site of the injection, or when general anaphylactic phenomena appear, something must be done. The results in 100 consecutive cases of insulin allergy considered elsewhere[2] are summarized here. In 8 cases spontaneous desensitization occurred during regular treatment. In 64 cases there was relief from the irritation following use of insulin from a different source, either insulin made by a different manufacturer, or made by the same manufacturer from the pancreas of a

different species.* In most of these cases spontaneous desensitization might have occurred eventually if nothing had been done, but the early relief given by changing the kind of insulin was significant. In 6 cases irritation from the injections continued, but was not serious enough to interfere with treatment. In 22 cases in which insulin was used only temporarily hypersensitiveness persisted.

Efforts to bring about desensitization deliberately have not been very satisfactory, but in 1 case of the last group, temporary desensitization to deal with an emergency was successful. A middle-aged woman who had had mild diabetes for 7 years required insulin temporarily on 3 occasions. When used first, after a pelvic operation, there was a local reaction. On the second occasion, when given at the time of treatment of varicose veins, there was an urticarial eruption accompanied by prostration for 3 days. It was needed again after an operation for empyema of the gall bladder, which caused such serious aggravation of diabetes that acidosis developed. An attempt at that time to administer ordinary insulin caused a general reaction with alarming symptoms. A solution of crystalline insulin, obtained from Dr. D. A. Scott, of Toronto, caused only a mild local reaction. It was administered in minute dosage at the beginning, the injections being repeated at short intervals and gradually increased. This resulted in desensitization, so that within 24 hours effective doses could be tolerated. The patient was thus rescued from threatening coma.

In none of the cases reported in a previous paper was there any interference with the effect of insulin on diabetes. Glycosuria and hyperglycemia were controlled with a dosage within the usual limits. However, in the recent case reported herewith there was unusual resistance to its action. Diabetes relatively refractory to insulin has been encountered with hemochromatosis[1] and under certain other conditions, but is extremely rare. We have been able to find records of only 4 cases in which resistance to insulin seemed to occur as a result of allergy, or in which this was considered as a possible explanation. One case was reported by Williams. Acidosis was present and continued until the kind of insulin used was changed. Karr, Kreidler, Scull and Petty had a patient who was given several hundred units daily for a long period without complete control of symptoms. The occurrence of skin reactions from the injections of insulin led to serologic tests, and the patient was treated with serum from a rabbit to which the patient's serum had been administered. Subsequently an abrupt change occurred so that diabetes became latent without treatment. Rudy reported the occurrence of diabetic

* Insulin specially made from the pancreas of sheep was supplied by E. R. Squibb and Sons through the courtesy of Dr. John F. Anderson. It was used in our investigation but did not prove to have practical value, since patients sensitive to commercial insulin from pancreas of hogs and cattle were sensitive to this. Eli Lilly Company also supplied special preparations of insulin for trial.

acidosis temporarily resistant to insulin in a case of urticaria. The fourth patient, Foerster's, had urticaria attributed to sensitiveness to insulin, also mild acidosis. Large doses of insulin were given without apparent benefit; in fact, the condition improved when the insulin was stopped although glycosuria continued.

Report of Case.—A woman, aged 55 years, was found to have mild diabetes in March, 1921. She neglected treatment until acidosis occurred in 1924. Insulin was then used temporarily and treatment with "neosynthalin" was later tried intermittently, but, as a rule, dependence was placed on dietary treatment alone. The patient usually had good health, although the urine frequently contained a small amount of sugar. When she came to The Mayo Clinic, April 6, 1932, the submaxillary lymph nodes were enlarged. This had appeared several weeks previously, when she was ill with a severe respiratory infection. The diabetes had been aggravated at the same time and glycosuria had continued so that treatment with insulin was begun in a dosage of 15 to 20 units daily. About 10 days later a mild local allergic reaction developed.

When the patient was first seen at the clinic she stated that the submaxillary swelling was subsiding, but 3 weeks later it appeared to be larger. A gland was removed from the neck, under local anesthesia, April 30, 1932. This was diagnosed lymphosarcoma, Hodgkin's type.

On the afternoon of April 30 the patient became seriously ill. In the evening she vomited repeatedly. Later marked prostration, difficulty in breathing and drowsiness developed. When she was seen at her home at 9 P.M. she was on the verge of coma, but was able to sit up in bed and answer questions. She was given 40 units of insulin at once and transferred to the hospital. More insulin was given, but the condition became gradually worse, and soon there was complete loss of consciousness. The carbon dioxid combining power of the plasma fell to 6 per cent by volume. The heart began to fail and the systolic blood pressure dropped to 80 mm. There was a sudden change in the heart action 4 hours after admission, and it was difficult to feel the radial pulse. Auricular fibrillation followed later. Injections of insulin were repeated at intervals, with the dosage increased. In 12 hours the patient had received 500 units with only slight response. The blood sugar remained high, and the carbon dioxid combining power of the plasma was extremely low. Sodium bicarbonate was administered once by proctoclysis and three times intravenously with benefit. The labored breathing became easier and the circulation improved. The patient opened her eyes and was able to take a drink, yet her condition remained critical.

About 12 hours after admission to hospital a diffuse urticarial eruption, with numerous large blebs, appeared over the patient's entire body. The possibility that the resistance to insulin was due to allergy was recognized. The kind of insulin used was altered, and a solution of crystalline insulin was then employed. One hundred and fifty units were given intravenously at once, followed by small doses at short intervals. There was an immediate change and the ketosis was soon overcome. The carbon dioxid combining power of the plasma, elevated somewhat by the treatment with soda, now rose to normal. The blood sugar was continuously elevated by injections of glucose solution given at intervals.

The patient seemed out of danger from diabetes, but the cardiac condition was serious. Profound prostration continued; the blood pressure was low; fibrillation was noted intermittently. Since the supply of crystalline insulin was limited, an effort was made to use commercial insulin. It was diluted and used in minute doses to begin with, the size of the dose being increased gradually. Some inflammatory reaction occurred at the site of

each injection. The carbon dioxid combining power of the plasma remained normal, but because of precautions to avoid hypoglycemia, which might affect the heart unfavorably, the blood sugar was permitted to remain high. The heart continued to fail and 4 days after admission death occurred. Toward the end even more caution was used in giving insulin. A blood test made 10 minutes before death showed that the blood sugar had risen to 500 mg. for each 100 cc. and the carbon dioxid combining power of the plasma had fallen to 36 per cent by volume. More insulin should have been given before this, but it would not have affected the outcome, since the patient was then moribund (Table 2).

TABLE 2.—DATA ON CASE REPORTED.

Date.	Insulin units.*	Time.	Blood sugar, mg. for each 100 cc.	Carbon dioxid combining power, per cent.
April 30	160 A	9.30 P.M.	536	19.2
		12.00	462	6.0
May 1†	340 A	1.00 A.M.	448	6.0
	178 T	2.00 A.M.	448	6.0
		3.30 A.M.	390	6.0
		5.30 A.M.	462	13.6
		7.15 A.M.	429	12.0
		9.30 A.M.	517	13.6
		10.30 A.M.	517	36.2
		12.30 P.M.	502	40.0
		3.00 P.M.	508	50.4
		5.00 P.M.	476	54.1
		7.30 P.M.	423	50.4
		10.30 P.M.	385	54.1
Total	518			
May 2	156 T	7.10 A.M.	370	56.0
	30 B	11.00 A.M.	429	60.5
		2.00 P.M.	429	48.5
		7.15 P.M.	400	54.1
		10.30 P.M.	361	54.1
Total	186			
May 3	64 T	8.00 A.M.	300	
	48 C	12.15 P.M.	353	
		4.30 P.M.	429	
		9.30 P.M.	435	
Total	112			
May 4	8 C	6.30 A.M.	500	36.2

* A, B and C varieties of commercial insulin; T, crystalline insulin.

† Three hundred cubic centimeters 5 per cent sodium bicarbonate solution given by continuous proctoclysis during the night; 400 cc. given intravenously at 12.30 A.M.; 500 cc. given intravenously at 9.30 A.M.

The postmortem examination disclosed an advanced degree of coronary sclerosis, with rather marked narrowing of all branches of the coronary arteries near their orifices. The muscle of the left ventricle revealed acute infarction, the infarcted portion extending into the septum and involving portions of the papillary muscles posteriorly. Approximately a third of the substance of the muscle was affected. Microscopically this infarcted zone was revealed as a region of necrosis with a margin of polymorphonuclear leukocytes and hemorrhage. Older fibrous foci were also present.

The gall bladder contained a large, single calculus, which completely filled the lumen. The wall of the gall bladder was thickened and increased in density. Surrounding this wall there was edema of the tissues, with beginning purulent infiltration. Examination of the neck failed to reveal any lymph nodes with involvement typical of Hodgkin's disease, but re-

examination of the lymph node removed 4 days before death confirmed the impression of a Hodgkin sarcoma. In the lungs there was bronchopneumonia, with beginning pleuritis in the dependent portions of both lower lobes. Occasional foci of fat necrosis were seen in the pancreatic fat.

Further minor details consisted of fine points of hemorrhage in the skin over various portions of the body, chronic tuberculosis of the hilus nodes of the lung, and advanced melanosis of the colon. Microscopic examination of the pancreas revealed only minor changes in the islands, which might point to degenerative conditions consistent with diabetes.

The factor immediately responsible for death was the cardiac infarction.

Comment. The sudden development of diabetic coma in a case in which treatment previously had been successful, and the lack of response to huge doses of insulin, were obviously the result of interference with the action of the insulin administered. The existence of hypersensitiveness toward insulin, manifested by local irritation at the site of injection, and later by the appearance of urticaria and cutaneous blebs, points to an allergic phenomenon as the cause.

It is so rare for allergy to cause resistance to insulin that there are no rules to guide treatment under such circumstances. Five modes of procedure have been applied in this and other cases in which the problem has arisen: (1) Stop treatment with insulin, in the hope that spontaneous adjustment will take place. This may be attempted with a patient free from ketosis, or with ketosis of mild degree, as in Foerster's case, but would be foolhardy in the presence of threatening coma. (2) Increase the dosage of insulin to the point where it does become effective, as was done in Rudy's case. (3) Change the kind of insulin, as did Williams, using preferably solution of crystalline insulin in the hope that it may be tolerated. (4) Attempt desensitization, choosing the kind of insulin, if any, which is best tolerated, giving it in minimal doses at the beginning of treatment, then gradually increasing to effective doses as tolerated. (5) Endeavor to prepare a serum which will overcome the disturbance, as was claimed by Karr, Kreidler, Scull and Petty. In the case reported here, treatment was attempted by a combination of the third and fourth plans. The patient began to respond to the treatment, and might have recovered had it not been for the serious injury to the heart, which occurred when the acidosis was at its peak.

The infarction of the heart may be explained as a result of the abnormal lowering of the blood pressure, which resulted from the intense acidosis. The patient had sclerotic coronary arteries, and the high blood pressure usually present presumably maintained adequate flow through them. When the blood pressure fell the flow must have become sluggish so that thrombosis could readily occur.

The lymphosarcoma was another factor which would have affected the ultimate prognosis. Also, the biopsy complicated the situation. Diabetes is sometimes aggravated by even simple surgical pro-

cedures. Yet the extreme resistance to treatment manifested by the development of coma which was refractory to commercial insulin is attributed to the allergic phenomenon.

Summary. Allergic reactions to insulin have become less frequent but still occur in a significant number of cases. Serious symptoms are uncommon, and alteration of the action of insulin has seldom been encountered.

A report is given of a case of diabetes which became refractory to insulin because of allergy. Coma developed and at first could not be overcome with massive doses of commercial insulin. Treatment with solution of crystalline insulin brought about partial recovery, but death occurred four days later from cardiac infarction.

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ALLERGIC MIGRAINE.

II. Analysis of a Follow-up After Five Years.*

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In 1927 the author reported[1] 33 cases of migraine, 36 per cent of whom were relieved following the discovery and avoidance of allergenic foods. The presence of an allergic factor in many cases has been substantiated by several workers, notably Rowe,[2] Rowe and Richet,[3] Eyermann,[11] Balyeat,[4] and Beecher,[5] although very recently Coltman[6] reports that migraine due exclusively to sensitization was not observed in his series, studied from the allergic point of view. The present report is based upon 82 cases, all that the author has studied allergically up to the present. Nineteen were referred for examination only and I have been unable to follow them. The remaining 63 have been adequately followed over periods up to 11 years and form the material for this analysis.

In my analysis 5 years ago I reported 10 cases relieved on specific food avoidance. Five years later, 3 are dead but con-

* Read before the annual meeting of the Michigan State Medical Society at Kalamazoo, Mich., September 15, 1932.

tinued free of migraine until their death (Cases 6, 7, 10); 4 continue symptom free (Cases 2, 3, 4, 5); 2 report return of symptoms. The first (Case 1) has moved to a distance and has not been seen in 5 years. She now reports that the original foods still cause migraine but that she had other attacks of unknown cause. A few months ago she had 3 devitalized teeth extracted and has since been symptom free. The other case with recurrence of symptoms (Case 9) was relieved for 3 years, after which symptoms returned. She is an Armenian, does not speak English well, finds coöperation rather difficult and has had a long period of anxiety over financial reverses which recently culminated in the bankruptcy of her husband. The last of these 10 original cases has not been traced (Case 8). Seven either continue well or continued well until their death. Information is not available on 1 and the remaining 2 have had a return of symptoms which, however, can be at least partially explained.

Results in the present series of 63 are classified as: (*a*) excellent, (*b*) good, (*c*) fair and (*d*) no relief. *Excellent* means that on the avoidance of specific allergenic foods the patient remains entirely free from headache. *Good* indicates that on avoidance the individual is nearly symptom free but with occasional headaches, usually traceable to some other definite nonspecific cause. *Fair* indicates persistence of headaches in spite of the fact that the individual has demonstrated by trial that the specific foods will cause migraine: a specific allergic factor has been demonstrated, but its removal has not given relief.*

Of the 63 cases, 25 report excellent results, 7 good, 11 fair and 20 no relief. There is evidence of an allergic factor (fair, good and excellent), in 68.3 per cent; satisfactory results were obtained (good and excellent) in 50.8 per cent, and excellent results in 39.7 per cent. Since extraneous factors enter into the fair-result cases, the following analysis of good and poor results will not include the fair cases unless so stated. The good and excellent will be grouped together as "cases relieved," for comparison with "cases not relieved."

Of the 43 showing evidence of an allergic factor (good, fair and excellent), 35 have been followed for more than 1 year since testing, 18 for more than 5 years, 7 over 9 years and 1 for 11 years.

If we may obtain excellent results in 40 per cent, good results in 50 per cent and evidence of an allergic factor in nearly 70 per cent, it seems advisable to attempt an analysis to determine the reason for reported failure to do as well[6] and particularly in an effort to increase still further our percentage of good results.

Identification. The question might be raised, are we dealing with true migraine? The author has seen a few cases of headache due to

* Variations in the percentages of good results from allergic therapy in migraine recently reported[2,10] are presumably due to the selection of varying standards as measures of the adequacy of the treatment.

inhalant allergy indistinguishable from migraine, but these are not included. All of those reported have been cases of ingestant allergy. They are typical, hereditary, periodic headaches, often with associated nausea, vomiting and eye symptoms and sometimes influenced by the catamenia, in which refractive errors and other factors have been ruled out or controlled, and in whom the symptom has been present over a period of years. Unilateral distribution of pain, while frequently recorded, or recorded as recurring at times, has not been insisted upon as a requisite for the diagnosis of migraine.

Possibly it might be more appropriate to have designated this series "periodic or recurring sick headache," since hemicrania has not been considered a requisite, but the term has been used in its commonly accepted significance as "migraine headache." Moreover, as has been brought out by Rinkel and Balyeat,[10] unilateral localization is not necessarily a constant characteristic of migraine. Furthermore, most of the cases reported did describe unilateral localization at times. The term allergic headache[11] is not desirable since this is a designation that can be arrived at only after therapeutic trial and automatically eliminates the cases not relieved. It is a a *post-hoc-ergo-propter-hoc* diagnosis.

Clinical Data. *Nausea and Vomiting.* Of the patients, 85.2 per cent complained of nausea and 60.4 per cent of vomiting with their attacks. Only about half of the no-relief cases suffered nausea and vomiting, while 27 of the 32 that were relieved had nausea and about half had vomiting.

Eye Symptoms. Of the entire series of 63, 39.9 per cent had eye symptoms, manifested as follows: Scotoma, 3 cases; blindness, 4; hemianopsia, 1; extraocular palsy, 2; partial blindness, 5; blurring of vision, 2; eye symptoms (type not specified), 2. Seven of 32 relieved cases gave a history of eye symptoms. Eight of 20 not relieved did likewise.

Age of Onset. McClure and Huntsinger[7] found, in a series of 78 patients, that migraine begins before the age of 20 years in 83 per cent and before the age of 30 in 95 per cent. In this series the symptoms began before the age of 20 in 65 per cent and before the age of 30 in 91 per cent. Considering the relatively small number in both series this shows sufficient correlation for us to state that the age of onset in this series is characteristically that of migraine. (Table 1.)

TABLE 1.—AGE AT ONSET.

Before 10	33	65.7%	91%
11 to 15	5		
16 to 20	6		
21 to 30	17		
31 to 40	2		
41 to 50	3		
After 50	1		

Family History of Migraine. Among the 51 in whom the family history was recorded, 38 gave a family history of periodic sick headaches; 83 per cent of the relieved cases and 69 per cent of those not relieved gave a family history of migraine.

Sex. Fifteen were males and 48 females.

Catamenia. Of the 22 females that were relieved, 5 experienced exacerbation with the catamenia. Of the 16 not relieved, 2 gave a similar history.

Duration. The duration of the illness is recorded as from 2 to 55 years. The average duration in those relieved was 21 years, in those not relieved 15 years. Of the entire series the duration was recorded in 52. In 14 it had been less than 10 years; in 38, 10 years or more. Of the 26 who were relieved, 20 had had their migraine 10 years or more, 4 of them having had it for over 45 years. Of the 15 with no relief, 11 had had it for over 10 years.

Periodicity. In 48 of the 63 the periodicity was recorded. In 25 the headaches occurred 2 or more times each month; in 17, at intervals varying around 1 or 2 months; in 6, at longer, irregular intervals such as 2 or 3 times each year.

Allergic History. If migraine is partly or wholly allergic, our experiences would lead us to anticipate a history of other allergic manifestations in the individual and a family allergic history.

Over half, 33, recorded other allergic symptoms as follows: Asthma, 8 times; hay fever, 19; urticaria, 16; eczema, 9. Thirty gave a negative history for other allergic manifestations.

Complete family allergic history was recorded in 51. In 43 of these 51, family allergic manifestations were distributed as follows: Asthma, 12; hay fever, 14; urticaria, 5; eczema, 10; migraine, 38. Only 8 had a negative family history for other allergic symptoms or migraine.

Results. As had been stated, 50.8 per cent were relieved, 39.7 per cent entirely so; 68.3 per cent showed evidence of an allergic factor. The average duration of relief in the 32 relieved cases has been 4.4 years, ranging from several months to 11 years.

Twenty-one replied to the question whether they have found that, after having avoided the causative foods for a period of time, they now find that they can eat them with impunity; 7 (one-third) find that they must continue to avoid them. Two-thirds can eat them at times. The period of avoidance among those who were able to return to these foods ranged from 1 to 9 years. On the other hand, of those who still have symptoms from prohibited foods, 1 has avoided for 10 years, 1 for 6 years, 2 for 5 years and 1 for 4 years. The obvious interpretation is that some appear to lose their sensitizations, while in others it tends to persist indefinitely, certainly as long as 10 years.

Replies such as the following are illustrative of those who find that they can eat the forbidden foods at times: Mrs. B. can eat

all of the forbidden foods except fish and cabbage. With Mrs. F., the foods cause symptoms only when she is fatigued. Miss F., sensitive to wheat, can sometimes eat it as long as from 3 to 5 weeks but eventually develops headaches therefrom. Mr. G. states that wheat or beans eaten at 1 meal will cause no symptoms but will do so if taken for 6 meals straight. Miss O. can eat all forbidden foods in moderation but not in excess.

Analysis of Factors Influencing Results. *Age.* We find that age is not a factor. Four of the relieved patients were over 60, 1 over 70 years. The curves of age distribution are entirely comparable in the relieved group and those not relieved; in both the peak is at ages 30 to 35 years.

Duration. Duration does not appear to be a great factor. The maximum duration in the relieved group is 55 years (2 cases); in those not relieved, 45 years. The average duration is greater in the relieved group (21 years) than in the unrelieved group (15 years).

That age and duration are not factors influencing results is what we would anticipate if migraine were an allergic manifestation. It is to a great extent the case in the other allergies and is what one would expect in view of the fact that the condition is not associated with permanent organic alterations. If the cause can be discovered and removed one would expect return to normal no matter what the duration, provided secondary degenerative changes have not occurred.

Periodicity. One would expect that, the less frequent the attacks, the easier it would be to find the offending cause. This is borne out in limited degree in our analysis. Of those in whom the periodicity was measured in weeks 26 per cent failed to improve. Of those in which it was measured in months 29 per cent failed to improve. Of those having irregular attacks at much longer intervals only 17 per cent failed to improve. With longer intervals between the attacks the cause may be more readily discovered.

Sex. Here we meet with a surprise. Of the females 48 per cent were relieved and of the males 60 per cent. Results were distinctly better among the males. The reason for this is conjectural, but the author would suggest that a chief factor is the greater ease with which a man may adhere to his diet. The woman is constantly subjected to temptation in the kitchen, at card parties and the like, while the man at home must eat what is placed before him. In the restaurant he scans a long menu with his specific prohibitions in mind.

Catamenia. Of 7 women having headaches with the catamenia, 5 were relieved and 2 were not relieved. The catamenia acts only as a nonspecific exciting factor in allergically predisposed individuals; if the allergy is controlled the pelvic state will not interfere with good results.

Constipation. The same remarks apply to this factor. Twenty-five stated definitely that they were chronically constipated. Of these 13 were relieved, 4 had fair results and 7 were not relieved. No material change was made from the patient's previous method of controlling his constipation.

Blood Pressure. Systolic blood pressure in relieved cases ranged from 100 to 192; in those not relieved, from 90 to 200. Of 23 relieved cases only 3 had blood pressures below 110 and only 5 were above 145. The blood pressure range was such as is usually observed in office routine.

Chief Complaint. Some patients came for study primarily because of the migraine. Others came for different reasons and mentioned their sick headaches incidentally. The percentage relieved was the same in both groups.

Inheritance. Of 29 with a family allergic history or family history of migraine 51.7 per cent were relieved. Of 9 without family allergic history only 33.3 per cent were relieved. This limited evidence suggests that the stronger the family history of allergy or migraine, the more likely are we to find an allergic factor, thereby obtaining relief.

Other Allergic Manifestations. Of 24 without other allergic manifestations 37.5 per cent were relieved; of 21 showing other allergic manifestations 62 per cent were relieved. Here again the inference is that confirmatory evidence of an allergic state increases the probability of good results.

Gastrointestinal Complications. The information available on this question is not sufficiently detailed to be of great value. Gastrointestinal studies were limited to history and physical examination with occasional gastric analysis, biliary drainage or Roentgen ray studies. Since these were not routine no statistical analysis can be attempted. In 2 a diagnosis of visceroptosis was made. One obtained relief, the other no relief. Four suffered from a complicating colitis, 2 obtained relief and 2 none; 4 had gall bladder disease, of whom 1 was not relieved, 1 obtained fair results and 2 were relieved without surgery.

Nonallergic Factors. In Table 2, Column 1, we find listed, by number of times mentioned, the reason given by good-result cases for some persistence of their headache. In Columns 2 and 3 the same is recorded for the fair-result cases; Column 2 being the reasons assigned by patients, and Column 3 the explanation reached independently by myself prior to receiving their reports. Columns 4 and 5 provide the same information on those who obtained no relief. While some of these factors are more difficult to control than others, it is at once obvious that the more completely they can all be rectified, the better will be the ultimate results.

Character of the Skin Reactions. The interpretation of the skin reaction is probably the most important factor in obtaining results.

The author has emphasized elsewhere[8] the importance of attaching possible significance to the borderline reaction and to the delayed positive. Had these types of reaction been ignored in this series the results would have been far inferior.

TABLE 2.—NONALLERGIC FACTORS.

Reasons given for attacks.	In 7 good-result cases.	In 11 fair cases.		In 20 cases not relieved.	
		By author.	By patient.	By author.	By patient.
Unknown	..	4	1	11	3
Fatigue	5	..	..	..	8
Worry	1	1	1	..	4
Excitement	2	..	2	..	1
Nervousness	2	..	..	..	2
Constipation	3	..	3	..	3
Catamenia	..	..	1	..	1
Strong light	1	..	..	..	1
Sleeplessness	..	..	..	..	1
Hunger	..	..	..	..	1
Exertion	..	..	1		
Eyestrain	2	1	1		
Thyroid deficiency	..	1	1		
Noncoöperation	..	2	..	7	
Colitis	..	1	..	1	
Cholecystitis	..	1	..	1	
Tuberculosis	..	1			
Purpura	..	1			
Dust	1				
Tooth infection	1				

In 28 relieved cases the immediate skin reactions to the offending foods were positive in 10, being strongly positive in but 5. In 9 they were borderline, in 5 barely suggestive and in 4 the immediate reactions were negative. The immediate reactions were definitely positive in only a little over one-third.

The delayed reactions were read after 6 and 24 hours. In 3 of the 28 (10.5 per cent) the delayed reactions alone were positive, the immediate reactions having been negative. In 6 (21.4 per cent) the delayed reactions were the only definite positive ones, although the immediate reactions had been borderline or suggestive. In 10 (35.7 per cent) none of the 3 readings, the immediate or the 2 delayed, was stronger than borderline.

Roughly, therefore, of those who were relieved, about one-third gave positive immediate reactions, one-third positive delayed reactions of diagnostic significance, and one-third gave no stronger than borderline reactions throughout, which, however, were of diagnostic significance.

It is of special interest to note that among 18 who were not relieved, 8 or nearly half also gave positive reactions, 2 of which were strongly positive. One is tempted to conclude from this that even with those who received no relief from allergic therapy, allergy is probably actually playing a part.

Foods Responsible for Migraine. It is by now a matter of common experience that one may react positively by skin test to an allergen which will nevertheless not produce symptoms. In each case with the onset of treatment the patient was given a list of the positive and borderline reacting foods. One would expect that the patient would find that some of these foods produced symptoms while others did not. This would be especially true with the borderline reactions. Table 3, Column 1, lists the foods which the patient was advised to avoid. Column 2 lists those foods which the patient subsequently reported as actually causing migraine. This second listing is decidedly reduced. In all, 293 foods were listed for the patients on the basis of the skin reaction, and of these 140 were found responsible for symptoms.

TABLE 3.—FOODS CAUSING MIGRAINE.

	Positive reactors.	Caused trouble.	Discovered by patients, times mentioned.
Wheat	19	19	
Rye	1	1	
Barley	1	1	
Oat	3		
Rice	2	1	1
Corn	4	2	
Cocoanut	1	1	
Pineapple	1		
Onion	6	4	2
Asparagus	5	2	
Banana	10	5	
Ginger	7	1	1
Fig	1		
Buckwheat	1	1	
Walnut	2		
Pecan	3		
Spinach	4	1	
Beet	4		
Turnip	7	2	2
Cabbage	6	2	
Cauliflower	4	1	
Kohlrabi	1	1	
Brussels sprouts	1	1	
Mustard	2		
Raspberry	2	1	1
Strawberry	4	2	1
Apple	6	3	1
Pear	6	1	
Almond	3	1	
Prune	2		
Cherry	4		
Apricot	2	1	
Peach	5	1	2
Pea	13	8	
Kidney bean			
Peanut	13	9	
Blackeye pea			
Lima bean			
Bean	13	7	
Lemon	2	..	2
Grapefruit	3	..	1

	Positive reactors.	Caused trouble.	Discovered by patients, times mentioned.
Orange	4	1	1
Grape			
Cottonseed	1	1	
Okra			
Cocoa	12	8	
Tea	5	1	
Celery	10	2	
Carrot	10	1	
Sweet potato	4	2	1
Tomato	5	2	
Peppers	2	1	
Eggplant	1	1	
Potato	3	1	
Coffee	3	2	
Squash	6	1	
Cantaloupe	5	2	1
Watermelon	1	1	1
Cucumber	1		
Lettuce	6	4	
Animal Foods:			
Beef	1	1	
Veal	2		
Milk	9	9	1
Cheese	1	2	2
Egg	9	4	1
Chicken			
Pork	6	6	2
Lamb	4	2	
Sea Foods:			
Crab	..	..	1
Oyster	2	1	
Fish	2	2	
Sardine	..	..	1
Salmon	..	..	1
Tuna	1	1	
Shad	1	1	
Miscellaneous:			
Whisky	..	..	2
Acid foods	..	..	1
Chicken liver	..	..	1
Ice cream	..	..	2
Sweetbread	1		
Candy	..	..	8
Rabbit	..	..	1
Vanilla	1		

It is interesting to note that two of the chief offenders, wheat and milk, consistently measured up to the significance attributed to them by the skin tests. The same was true with pork. This is fortunate, since with wheat, milk and other foods eaten daily, the sensitization reaction furnishes a valuable aid toward their recognition.

The most frequent foods causing migraine, in order of importance (Columns 2 and 3), were found to be wheat, milk, peanut, chocolate, pork, pea, bean, onion, egg and banana, with a wide scattering of other foods. Sixty-two different foods were found definitely to cause headaches.

It is reasonable to anticipate that with the attacks reduced in frequency and with the patient on the alert he will himself discover additional foods causing his migraine, foods which had failed to react positively on testing. Column 3 lists these foods which were discovered by the patient, who had been advised to keep a food diary with this end in view. It is interesting to note that, with few exceptions, the foods in this particular list are such as are eaten only occasionally and could, therefore, be more readily discovered.

This is entirely analogous to the author's experience in a survey of 100 so-called nonallergic individuals, among whom were found 15 who had in the past suffered from headaches which they attributed definitely to certain foods. Here again the foods were such as are usually eaten infrequently and their recognition was thereby greatly facilitated. Had each been sensitive to several foods, or had they been so unfortunate as to become sensitive to foods eaten regularly, they too would have become chronic migraine cases. But, the cause having been recognized, they have practised avoidance, are symptom free and are considered nonallergic. Of the 15, 1 each was sensitive to peppers, cabbage, peanut, chocolate, cheese and egg; 2 each to cauliflower, onion and candy and 3 to watermelon.

The question of idiosyncrasy to candy is of great interest. Brown[9] has concluded that carbohydrate intolerance is a distinct factor in the causation of migraine. Many carbohydrate foods contain protein moieties to which one may be sensitive and which could explain apparent carbohydrate intolerance. But can we say the same of candy? Eight patients in the author's series found from experience that candy caused migraine. Could there be noncarbohydrate allergenic substances in their favorite candies? The author has no information as to the favorite candies, but it is of interest that of these 8 cases 2 were sensitive to chocolate, 1 to almond, 1 to cocoanut and 1 to peanut. The remaining 3 had not been found sensitive to any of the common ingredients of candies. This leaves the question in the air for the present, but strongly suggests that more thorough analysis might demonstrate that it is not the carbohydrate of the candy which is responsible for attacks.

Proposed Method of Study of Migraine Cases. In concluding, the author whould like to present a program for the systematic analysis of a case of migraine from the point of view of allergy.

1. Have a very comprehensive discussion with the patient, covering the details of the symptomatology, and careful questioning regarding other allergic manifestations in himself and in his direct family inheritance. Where such other evidences of allergy are demonstrated, the case should be studied with special intensity from the allergic point of view. There should be a listing of the frequency with which different foods are eaten. Onion, cabbage and egg, for example, may be eaten only occasionally by one person

but may be practically staple foods for another. After foods have been listed as to frequency, as daily, weekly, monthly or occasionally, a comparison of the lists with the stated periodicity of the attacks may give suggestive information. Remember, however, in this connection that sensitization is usually multiple in the chronic allergic. The discussion with the patient should also cover nonallergic factors such as fatigue, worry, excitement, catamenia, eye strain, etc.

2. Make careful sensitization studies in accordance with the latest approved methods, paying considerable attention to the borderline and delayed reactions. Two years ago a patient who had given 25 borderline reactions, and no strongly positive ones, informed the author that every one of the borderline reactors caused trouble. The author immediately suspected that suggestion was playing a part, although, knowing the patient, it was found difficult to believe. In view of the foregoing analysis, there was little doubt that she was correct.

3. Have another discussion with the patient explaining the findings and their significance, outlining the program and insisting upon the absolute necessity of coöperation. The experience that male patients do better than females illustrates the value of coöperation. One must be very positive in the outlining of the program. Eight years ago the author examined an asthmatic lady and, finding her sensitive to milk, advised that she eliminate this from her diet. She was not seen again professionally. A few weeks ago she said that during the last year she had left milk completely out of her diet and that she was now well. She remarked that now you could not make her touch a glass of milk, while up to a year ago she was so fond of it that she regularly drank many glasses daily. "But," I said, "it was 8 years ago that I told you to avoid milk." To which she replied, "I didn't think you were really serious. If you had said *positively*, I should have done it then."

4. Instruct the patient in the keeping of a food diary, to discover other causative foods which failed to show up on testing.

5. Make every effort to control nonspecific complicating factors, especially emotional and fatigue factors.

6. This is most important: Insist upon the absolute necessity for periodic supervision, of diminishing frequency if the case is progressing satisfactorily, but with annual checkups over a period of years, in an effort to discover and remove new factors, both allergic and otherwise, as they arise.

It is not the intention to imply in this discussion that every case of migraine is exclusively allergic. Migraine in the last analysis is but a symptom. But the author is firmly convinced that allergy is at least one factor in the vast majority of cases, and that with improved methods the results from allergic therapy, which are now most promising, will undoubtedly be still further improved.

Summary. The late results of the treatment of migraine from the standpoint of allergy are presented, on the basis of 63 cases, together with an analysis of the clinical data and the factors which seem to have influenced these results. A proposed method for the routine study of migraine cases is outlined.

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COMPARATIVE ACTIONS OF SYMPATHOMIMETIC COMPOUNDS: THE CIRCULATORY AND LOCAL ACTIONS OF THE OPTICAL ISOMERS OF META-SYNEPHRIN AND POSSIBLE THERAPEUTIC APPLICATIONS.*

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In a recent paper[1] we pointed out the high order of activity of racemic meta-synephrin (metahydroxyphenyl-1-methyl-amino-2-ethanol-1) as a pressor drug and its low relative toxicity, and suggested that it might have therapeutic value. Recently, we obtained the levo- and dextro-isomers of this compound and its ketone, through the coöperation of Frederick Stearns & Co. The circulatory actions of these isomers have now been studied with the aim of determining their pressor efficiencies and mechanisms and some other actions, and of comparing them with the racemic mixture, previously reported.[1] The opportunity has also been taken to investigate various actions of meta-synephrin in human subjects, and to indicate its possible field of therapeutic usefulness.

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The racemic and dextro-compounds and the ketone were used in the form of hydrochlorids, while the levo-isomer was used as the tartrate and hydrochlorid. In comparing the activity and dosage of the levo-compound with the others, a correction must therefore be made for the lower meta-synephrin content of the tartrate salt. The levo-meta-synephrin base was reported by the manufacturers to have an optical rotation of −55.33 degrees at 20° C., while the dextro-base had +50.4 degrees. The dextro-base was, therefore, not entirely free of the levo-form. The corrected melting points were as follows: Levo-tartrate, 168° C.; dextro-hydrochlorid, 141.8° C.; racemic hydrochlorid, 142.2° C., and ketone hydrochlorid, 224.6° C.

Circulatory Actions. Cats. The control blood pressure and the pulse rate changes were recorded by the usual methods in urethanized cats, atropin being previously injected to permit elicitation of full pressor responses. Levo-synephrin tartrate was injected intravenously in doses ranging from 0.025 to 0.075 mg. per kilo, with resulting blood pressure increases of from 27 to 82 per cent. In 9 cats, the ratio of pressor activity of this isomer to the activity of epinephrin was a median of 5.15, range from 2 to 10. When this is expressed in terms of the hydrochlorid salt the ratio becomes 4.3. The dextro-isomer was much less active, doses of 0.5 to 1.5 mg. per kilo intravenously giving blood pressure increases ranging between 21 and 72 per cent. The median ratio of activity to epinephrin of this compound was 184, with a range of from 50 to 400. From these two ratios the racemic meta-synephrin would be expected to have an activity of about 8.5. The ratio of activity to epinephrin of the racemic, which was 5.6[1] is greater than can be accounted for by an additive action of the two isomers. This might be interpreted as evidence of a sensitization occurring in the racemic mixture. However, this cannot be accepted unreservedly, since the sum of the average deviations of the individual ratios from the two means is about equal to the observed differences between the means. The differences found are therefore statistically unreliable. The ketone was rather weak and variable in producing rises of blood pressure. The ratios of activity to epinephrin ranged between 224 and 714, with a median of 433. This low activity was in keeping with that of the other ketones previously reported by one of us.[2,3,4]

The duration of the pressor response to the two isomers was similar to that of the racemic form described previously,[1] that is, about 10 minutes. Constant responses were obtained to repeated injections if complete recovery of the blood pressure was allowed after each injection. The pulse rate was not altered by the levo-compound, but was increased an average of 10 per cent by the dextro-compound, and 14 per cent by the ketone. Since these cats were atropinized and had rapid pulse rates, the changes observed

do not necessarily indicate what the responses might be under other conditions.

In order to study the mechanism of the circulatory stimulation, the cats were cocainized by our usual technique.[5] This procedure increased the average pressor responses to a given dose of epinephrin from 32 per cent (control) to 59 per cent, *i. e.*, almost doubled it. At the same time, the average control response to the dextro-isomer, or 34 per cent rise of blood pressure, was unaltered, and the average response to the ketone was practically unchanged (from 19 [control] to 17 per cent) by the cocainization. But with the levo-compound the effect was different; the average control rise was 47 per cent, before the cocain, and after cocain it was greatly increased, *i. e.*, to 78 per cent. That is, there was almost as much sensitization to this levo-isomer as there was to epinephrin itself. Such sensitization by cocain to a compound not containing the catechol nucleus is quite unique, since there is no other noncatechol compound known to us with similar reaction. It may be that the suggestion of a sensitized response of the racemic mixture, previously noted by us,[1] may have been a true effect partially masked by the presence of the dextro-isomer.

Ergotamin* was injected intravenously in an average dose of 0.7 mg. per kilo, which sufficed to paralyze the sympathetic vasoconstrictors; the average control, or 48 per cent, rise of blood pressure after epinephrin was reversed to a fall of 21 per cent. The average control rise of 55 per cent after levo-meta-synephrin was decreased to an average rise of 21 per cent, but was not reversed. Similarly, the average pressor response to the dextro-isomer fell from an initial increase of 42 per cent to an increase of 30 per cent, and to the ketone, from an initial increase of 21 per cent to an increase of 4 per cent. All the ketone responses were unusually variable, because of the low order of activity of this drug, and hence are not especially reliable.

From the results obtained it is seen that the pressor actions of these meta-synephrin compounds were affected by either cocain or by ergotamin; but none of the compounds was both sensitized by cocain and reversed by ergotamin, or was unaffected by both these alkaloids. Hence, these isomers did not act as pure sympathicotropic, or as musculotropic, stimulants,[6] but rather were mixed in their actions, similarly to arterenol and some other compounds previously described.[2]

Patients. To determine the possible clinical usefulness of the pressor effects of racemic meta-synephrin, this compound was administered by various routes to patients, the changes in blood pressure, pulse rate and symptoms, if any, being observed until recovery to the normal condition occurred. In 7 patients intra-

* Ergotamin was used in the form of Gynergen-Sandoz, supplied by the manufacturer.

muscular injections of total doses of from 5 to 10 mg. caused prompt rises of systolic blood pressure, averaging 14 mm. for the 5-mg. dose and 36 mm. for the larger doses. The diastolic pressures were also increased, but to a lesser degree, average 23 mm. The pressor response began in 4 minutes, reached a maximum in 9 minutes, and required an average of over 45 minutes for return to the control level. Thus, there was a very persistent vasomotor stimulation. During the height of the rise of blood pressure, the pulse rate was slowed moderately, as would be expected from the action on the vagus.

The same dosages of meta-synephrin were injected subcutaneously in 14 patients. The average maximum systolic rise for the entire group was 30 mm., and the diastolic rise, 13 mm. The rises of blood pressure began in 8 minutes, reached the peak in 20 minutes, and returned to normal after 80 minutes. The vasomotor stimulation after subcutaneous injection was therefore not quite as prompt as after intramuscular injection, but was almost as great in degree and about twice as persistent. It is obvious, therefore, that this drug, in the doses injected, is capable of producing well marked and sustained rises of blood pressure. It might, therefore, be a desirable remedy in those conditions requiring circulatory stimulation, such as collapse, hemorrhage, accidents of anesthesia and spinal anesthesia, etc. There were no obvious deleterious effects from the doses employed, except possibly in 2 or 3 of the patients, who had especially marked circulatory responses, in whom there was precordial discomfort at the height of the blood pressure rises. Such discomfort is a common accompaniment of the pressor responses to epinephrin and ephedrin, and is not peculiar to meta-synephrin.

The responses to oral administration of the racemic compound were determined in 15 patients at bed rest, who received the required doses in capsules. The minimal effective dose was about 120 mg., or approximately 2 mg. per kilo. The maximum dose administered was 300 mg. or 4.1 mg. per kilo. Throughout this range of doses there was some variation in the degree of pressor responses in individual patients, as might be expected. However, the systolic pressure increased an average of 23 mm., for the entire group of patients, and the diastolic, 14 mm. Thus there was an increase in pulse pressure at the time of the maximum pressor response, but the pulse rate compensated for this increased by a slowing of 18 beats per minute (average). Calculation of the cardiac output by the formula of Liljestrand and Zander[7] showed that there was an average maximum decrease of 21 per cent in cardiac output, due entirely to the greater degree of slowing. The highest rise of blood pressure observed was 89 mm., which occurred 2 hours after the administration. The onset of the pressor response was usually prompt, the peak occurring after about 30 minutes. At the end of

2 hours the blood pressure was still elevated 11 mm. (average), but some very persistent elevations lasting over 5 hours were obtained. Hence, the pressor response was of fairly long duration.

An especially noteworthy result was the absence of general symptoms during even the highest elevation of blood pressure. The most marked symptom observed was little more than an awareness of increased cardiac activity, so that, for all practical purposes, it can be said that this drug was free of the unpleasant side-actions characteristic of ephedrin.

Levo-meta-synephrin hydrochlorid was also tested by oral administration. The initial dose was half that of the racemic compound, but this dose was increased in successive groups of patients until a pressor response was obtained comparable to the average response of the group who received the racemic compound. It was found that 2 mg. of the levo-compound per kilo, or from 120 to 140 mg. total, gave the same average pressor curve as about 3.5 mg. of the racemic compound. That is, the racemic compound was somewhat more active than would be expected from its levo- content. The relative activity of these two isomers given orally in man therefore agrees with that observed after intravenous injections in cats, described above. The results with oral administration may be summed up by saying that from about 200 to 300 mg. of the racemic synephrin, or from about 120 to 140 mg. of the levo-synephrin, may be given by mouth with the expectation of producing a well marked rise of blood pressure which may persist for over 2 hours. This vasomotor stimulation is accompanied by either no symptoms at all, or much less disturbance than would be caused by an equipressor dose of either epinephrin or ephedrin. Meta-synephrin, therefore, has definite clinical pressor actions, which may be of therapeutic value when the drug is given orally, similar to, but more persistent than, when it is injected.

Antichemotic Effects in Rabbits. Epinephrin, tyramin, and some other compounds[8] have the power partially or completely to prevent local inflammatory edemas. In the present study we determined the anti-edemic actions of meta-synephrin by observing its effects on the degree of swelling and the time of development of chemosis after the application of mustard oil to the conjunctiva in rabbits. Solutions of mustard oil, ranging in strength from 5 to 100 per cent, were made in olive oil. Each of 11 rabbits received 2 drops of a given concentration in one conjunctival sac and the progress of the responses was recorded until recovery set in. After an interval of several days each animal was given 2 subcutaneous injections, 2 hours apart, of 5 mg. per kilo of levo-meta-synephrin. With the first injection the same number of drops of the same solution of mustard oil as used for the control was dropped in the previously untreated eye. The responses were then compared with the control to determine whether the meta-synephrin modified the course of the reaction.

In the 6 rabbits that received concentrations of from 30 to 100 per cent mustard oil, there was only a slight inhibitory effect of the drug on the chemosis. In 4 of these rabbits the effect was indicated by a small, but definite, decrease in the degree of swelling, or a delay in the development of the maximum response. In the other 2 rabbits the conjunctival responses were about the same as in the controls. These concentrations of mustard oil were sufficiently strong to produce a severe degree of irritation, which would require a very powerful antagonist; but meta-synephrin was almost ineffective. In the 3 rabbits receiving the weaker concentrations of mustard oil, namely 5, 10 or 20 per cent, an antagonism was clearly demonstrable. Meta-synephrin delayed the development of chemosis from 1 hour (time for maximum effect in controls) to 3 hours, and decreased greatly the degree of swelling. With the 5 per cent concentration of mustard oil, the meta-synephrin completely prevented the chemosis. Therefore, meta-synephrin exerted a definitely antagonistic action on the milder degrees of chemosis.

Topical Applications in the Human Nose and Throat. Because of its power to constrict bloodvessels, a possible therapeutic field for usefulness of meta-synephrin would be for local application in the nose and throat to shrink congested mucosæ, relieve turgescence and facilitate drainage. Epinephrin and cocain have been established as useful agents for these purposes for many years. Epinephrin, however, is apt to cause an increase in swelling after the initial period of vasoconstriction, and the use of cocain has serious drawbacks, such as the possibility of addiction, and the unpleasant or dangerous systemic reactions which may follow its use. In the last few years ephedrin has sprung into prominence for these local uses. However, there are also several disadvantages in its local effects, such as the almost universal production of pain and irritation, with secondary swelling and engorgement, and the occasional unpleasant systemic reactions. Recently we suggested the use of *para*-synephrin locally in the nose and throat,[9] as a result of studies in the Stanford Division of Oto-rhino-laryngology. This compound was as effective, in appropriate concentration, as previously used drugs, and was definitely less irritating than ephedrin. Since *meta*-synephrin has 21 times the pressor (vasoconstrictor) activity of the *para* compound,[1] it seemed desirable to test its local actions upon the nasal mucosæ.

Solutions of 0.5, 1 and 2 per cent were made in a physiologic saline solution containing 0.05 per cent chlorbutanol as a preservative. These solutions were instilled, sprayed or applied on a pack into one nasal cavity, while the other side was similarly treated with a 3 per cent solution of ephedrin as control. It was found that the 0.5 per cent concentration of meta-synephrin produced a good constriction in 2 minutes, indistinguishable from that of the 3 per cent ephedrin. This constriction lasted 2½ hours, or ½ hour longer than

the ephedrin. With the 1 per cent solution the constriction was maximal, occurred within 1 to 2 minutes, and persisted up to 4 hours, or about double the duration of ephedrin action. Use of the 0.5 and 1 per cent concentrations was accompanied by no detectable irritation or symptoms. A 2 per cent solution acted in ½ minute, with a 4-hour duration, but with slight irritation.* These results indicate that the meta-synephrin, in 1 per cent strength, cause intranasal shrinkage as much as, or more than, a 3 per cent solution of ephedrin, and apparently without irritation. Thus far we have seen no deleterious effects from its use, and no reactions, either systemic or local, so that it would appear to have a definite advantage over ephedrin for topical applications. As compared with para-synephrin, the 1 per cent meta-synephrin gives a more complete shrinkage than the para-compound in stronger solutions, and would therefore be the drug of choice. Observations along these lines are being continued and will be reported elsewhere in due time.

Use in Infiltration Anesthesia. Another use for the vasoconstrictor action of meta-synephrin might be as an adjuvant to local anesthetics in infiltration anesthesia. An indication of the possible usefulness of the compound was obtained by testing the power of various strengths of meta-synephrin to prolong the effects of procain. For this purpose 1 per cent procain solutions were made up so as to contain levo-meta-synephrin in 6 different concentrations, ranging between 0.01 per cent and 0.2 per cent. Higher concentrations of meta-synephrin were not tried since even with 0.2 per cent a full systemic dose would be contained in only 5 cc. of the anesthetic mixture. As controls, 1 per cent procain alone, 1 per cent procain with 0.001 per cent or 0.002 per cent epinephrin, 0.002 per cent epinephrin alone, 0.2 per cent levo-meta-synephrin alone, and physiologic saline solution were used. Two-tenths of 1 cc. of each of the 12 solutions was injected with aseptic precautions into separate squares marked off on the skin of the forearm of a subject. The appearance of a wheal was considered as good evidence of a satisfactory injection. Each injected area was tested for anesthesia at brief intervals until sensation returned to normal. The subject on whom the observations were made, and who had, of course, to judge whether anesthesia was present or not, was kept in ignorance of the particular solution injected in each area. Several such experiments were carried out on 3 subjects; the accompanying table shows the average times of duration of anesthesia with each solution.

It may be seen from this tabulation that procain alone produced a local anesthesia lasting an average of 25 minutes, while the other control solutions gave more transient effects. With the procain-meta-synephrin mixtures, duration of anesthesia was about doubled.

* We are indebted to Drs. G. I. Roberts and F. W. Borden for making these observations.

There was, however, no increase in efficiency with the stronger solutions of the meta-synephrin, so that apparently even the weakest concentration tested produced the maximum effect obtainable from such a mixture. By contrast the weaker epinephrin-procain solution (0.001 per cent) gave a duration 3 times that of the procain alone, and the stronger epinephrin solution (0.002 per cent) gave a duration 5 times as great. It is, therefore, apparent that the synephrin has power to enhance procain anesthesia, but is weaker than epinephrin in this respect. The main advantage of the synephrin would appear to be that it is stable in solution and, hence, could be used in the ready-made anesthetic solutions, instead of requiring addition just before use, as is the case with epinephrin.

TABLE 1.—AVERAGE DURATION OF ANESTHESIA.

Solution used.	Duration in minutes.
Physiologic saline solution	8
l-m-synephrin, 0.2 per cent	11
Epinephrin, 0.002 per cent	20
Procain, 1 per cent	25
Procain, 1 per cent + l-m-synephrin, 0.01 per cent	50
Procain, 1 per cent + l-m-synephrin, 0.025 per cent	41
Procain, 1 per cent + l-m-synephrin, 0.05 per cent	42
Procain, 1 per cent + l-m-synephrin, 0.075 per cent	49
Procain, 1 per cent + l-m-synephrin, 0.1 per cent	52
Procain, 1 per cent + l-m-synephrin, 0.2 per cent	44
Procain, 1 per cent + epinephrin, 0.001 per cent	72
Procain, 1 per cent + epinephrin, 0.002 per cent	133

Effect on Blood Sugar. One of the actions of epinephrin, or of ephedrin, is to raise blood sugar, which may be of value in combating hypoglycemic conditions. Tests were made to determine whether meta-synephrin shared this property. Three patients were injected with 7.5 mg. and 2 with 10 mg. of racemic meta-synephrin, subcutaneously, after a 12-hour starvation period. Blood samples were taken at ½-hour intervals for 3 hours. An average blood pressure rise of 30 mm. resulted from the injections and lasted an average of over 100 minutes. But in none of the patients was there the slightest rise of blood sugar during the 3-hour period of observation. Dr. Myron Heyn has informed us in a personal communication that 6 mg. of the drug per kilo subcutaneously will produce increases of blood sugar of about 40 mg. per cent in rabbits. Since the dosage of 0.15 mg. per kilo used in our patients approached the maximum desirable from the standpoint of the circulation, it is apparent that the dose required for hyperglycemia, as seen in the rabbit, would be too great for use clinically. Therefore, it may be concluded that, from the therapeutic standpoint, meta-synephrin cannot be of use for its effect on the level of blood sugar.

Influence on Allergic Reactions. Anaphylactic Shock.* In order to test the power of meta-synephrin to antagonize severe anaphyl-

* We are indebted to Drs. Samuel H. Hurwitz and A. L. Wessels of the Stanford Allergy Clinic for the observations described in this section.

actic shock, experiments were made on sensitized guinea pigs. Eight guinea pigs were sensitized by injecting horse serum 3 weeks previously. On the day of the test, 3 animals were given 3 mg. per kilo, and 5, 14 mg. per kilo of racemic meta-synephrin, intramuscularly. From 15 to 30 minutes later, they were given an intravenous shocking-dose of the antigen. Of the 8 guinea pigs, 6 (75 per cent) died within 10 minutes after the injection of the antigen, the lungs at autopsy showing the typical distention of fatal anaphylactic shock. The 2 remaining animals showed severe symptoms, but recovered. In several control series of guinea pigs, treated in the same way except for the meta-synephrin, the percentage mortality ranged from 65 to 80 per cent. Therefore, meta-synephrin was not effective in diminishing the mortality, or the symptoms, of anaphylactic shock in guinea pigs.

Asthma and Urticaria. Further tests were made on allergic reactions in 5 patients. In 3 of these, spontaneous attacks of asthma of the typical allergic type were present, associated with a previously demonstrated specific sensitivity to certain antigens. The other 2 patients had the same type of sensitivity, but their asthmatic attacks and urticaria had been induced by the injection of specific antigens during the course of a desensitizing treatment. The dosage of racemic meta-synephrin used varied from 10 mg. as a single dose to 2 doses of 20 mg. each, all being given intramuscularly. In none of these cases was the bronchospasm or urticaria ameliorated to a perceptible degree by the meta-synephrin. However, epinephrin, injected subsequently, promptly terminated the attacks in the usual manner. Apparently, therefore, meta-synephrin lacks the power to antagonize the symptomatic manifestations of anaphylactic shock in patients. This might have been predicted from the results recently obtained by Dr. Martha James, in this laboratory (to be published later), namely, that meta-synephrin failed to relieve the bronchospasm induced in perfused guinea pig lungs by typical bronchoconstrictor drugs. Thus there is no satisfactory experimental basis for using meta-synephrin in allergic conditions, unless it might act as a circulatory stimulant in case of collapse.

Discussion. The results described have established a number of interesting facts. From a fundamental standpoint, one of the most intriguing of these is the demonstration of cocain sensitization to the pressor action of levo-meta-synephrin, and a failure to do so to that of the dextro-isomer. Inasmuch as these differences are qualitative, and probably not merely quantitative, here is a situation where optical isomerism modifies the fundamental nature of a pressor response, and not just its degree of intensity. This is contrary to a common conception of the relation of chemical structure to the pharmacologic action of such compounds, namely, that the chemical radicals determine the mechanisms of their actions. It has been previously pointed out by one of us that tissues show pronounced

selectivity of response to optical isomers, in the group of sympathomimetic amines[3,4] and in the cocain[10] group as well. The demand of the tissues that levo-isomerism be present, if maximum pharmacologic activity is to be obtained, stands as a challenge to the chemist to supply the chemical basis for such selectivity. Studies directed toward the solution of this problem would be of great importance for understanding of the cause and nature of direct tissue responses to drugs, and even of the indirect responses from stimulation of the nerves themselves.

Of interest from the therapeutic standpoint is the high order of circulatory stimulant (pressor) efficiency of meta-synephrin, whether the drug is given subcutaneously, intramuscularly or orally. At present there is no other available compound which, when injected in the small dose of 10 mg. or less, will produce clinically a sustained rise of blood pressure, such as was observed by us. Small doses of epinephrin will produce similar rises, but they are less sustained. We have previously shown[1] meta-synephrin to have a margin of safety 8 times that of epinephrin in equipressor doses, or 45 times the margin when figured from the absolute weight of the drugs. Ephedrin will produce a rise somewhat longer in duration, but requires at least 5 times the dose; it has deleterious side actions on the heart,[11] its administration cannot be repeated freely, and it is apt to cause unpleasant symptoms. None of these objections hold for the meta-synephrin. Postpituitary extract will produce a rise of blood pressure similar in height and duration to meta-synephrin, but pituitary induces a complicating coronary spasm[12] and cannot be used repeatedly. It would seem, therefore, that racemic or levo-meta-synephrin would be especially valuable in those conditions requiring maintenance of adequate levels of blood pressure, as in spinal anesthesia, operations, shock and collapse with circulatory failure.

The other valuable clinical application of the drug should be as a topical agent in the treatment of congested or turgescent membranes in the nose and other suitable regions. The property of shrinking these membranes is not peculiar to meta-synephrin, but is shared by many compounds. However, this new drug seems to cause the shrinkage with a minimum or no side actions or symptoms. Therefore, in the opinion of our clinical colleagues, who have critically evaluated its merit by parallel controls, it would seem to be definitely superior to epinephrin and ephedrin.

Consideration should also be directed to the comparative merits of meta-synephrin and the para-isomer previously studied by us.[4,9] The conclusions from those studies were that para-synephrin could increase blood pressure in patients when it was injected intramuscularly in doses of 200 mg. or more. Meta-synephrin, by comparison, produces equally high and more persistent rises with 10 mg. doses. Subcutaneous and oral administrations of para-synephrin were inef-

fective. With the meta compound, subcutaneous injection is almost as efficient as is the intramuscular, and oral administration produces excellent rises, which are lacking completely with the para-isomer. Both are superior drugs for local application in the nose, the meta-compound producing an equal degree of action, but in lower concentrations. It follows that meta-synephrin possesses all the desirable clinical actions of para-synephrin, and to a greater degree, together with certain advantages. Therefore, it may replace the para-compound completely as a therapeutic agent.

Conclusions. 1. The levo- and dextro-isomers of meta-synephrin (meta-hydroxyphenyl-1-methylamino-2-ethanol-1), the racemic mixture, and the ketone were studied as to their pharmacologic actions and possible therapeutic uses.

2. All these compounds raised the blood pressure when given intravenously to atropinized cats, the ratios of activity of the hydrochlorid salts to epinephrin hydrochlorid being: levo-isomeric 4.3, racemic 5.6, dextro-isomeric 184, and the ketone 433.

3. The pressor responses to levo-meta-synephrin were sensitized by cocain, whereas the responses to the other compounds were unaffected. Paralysis of the sympathetic vasoconstrictors by ergotamin, which resulted in reversal of epinephrin action, decreased but did not similarly reverse the pressor responses to the meta-synephrin compounds. The combined results in cocainized and ergotaminized animals showed that these meta-synephrin compounds did not exert pure sympathicotropic actions as does epinephrin.

4. In patients, doses of from 5 to 10 mg. of racemic meta-synephrin hydrochlorid, injected intramuscularly or subcutaneously, caused persistent rises of blood pressure, without serious or unpleasant side actions. Oral administration of the levo-compound or racemic mixture in total doses of from 120 to 140 and 200 to 300 mg., respectively, caused increases in blood pressure, which were well sustained for 2 or more hours.

5. Meta-synephrin has a slight antichemotic action when given subcutaneously in large doses to rabbits.

6. Applied locally in the nose and throat, meta-synephrin proved to be a valuable decongestive drug, since it promptly reduced swelling and edema without irritation or after effects.

7. When added to procain solutions in maximum concentrations, meta-synephrin doubled the duration of local anesthesia produced, whereas epinephrin trebled it.

8. Meta-synephrin had no demonstrable effects on the level of blood sugar, allergic reactions and bronchospasms in experimental animals or patients.

9. The main field for clinical usefulness of meta-synephrin would seem to be as a systemic circulatory (pressor) stimulant, and as a locally acting vasoconstrictor on mucous membranes, as in the nose. For these purposes the racemic and levo-meta-synephrins should be of practically equal value, if used in equivalent dosage.

10. Meta-synephrin has all the demonstrated therapeutic actions of para-synephrin and to a higher degree, with the added advantage of being effective orally; therefore, it should be able to replace the para-synephrin as a medicinal agent.

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BLOOD PRESSURE IN YUCATECANS.*

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Blood pressure levels have long been used as an index of health or disease. Certain levels have been evolved as standards for normal pressures, and readings above and below these levels are regarded as abnormal. Many things have been shown to influence blood pressure levels, but nearly always these factors have been within the individual himself, for example, the vascular and cardio-renal efficiency or the normal or abnormal functioning of the endocrine glands, and but very little account has been taken of the environmental factors. A study of the influence of environment might lead to a more thorough understanding of some of the underlying causes of abnormal blood pressures.

It has long been the general impression that in tropical environments the general level of blood pressure is lower than in temperate or cold regions. While on a medical expedition to Yucatan during the summer of 1931, the author had the opportunity of mak-

* The observations on which this paper is based were made during the summer of 1931 by the "Third Medical Expedition to Yucatan," which was organized by the Department of Tropical Medicine of Harvard University and which worked under the auspices of the Carnegie Institution of Washington. The data will be more fully presented in a volume entitled, "The Peninsula of Yucatan. Medical, Biological, Meteorological, and Sociological Studies," by George Cheever Shattuck, *et al.*, which is to be published by the Carnegie Institution of Washington. In the same volume will be presented other data on blood pressure gathered independently in Yucatan by Shattuck.

ing a large number of blood pressure readings on Yucatecans of all ages.

As used in the text, the name Maya refers to that tribe of Indians living in Yucatan; Mestizo to a male of mixed blood, usually Mayan and Spanish, and Mestiza to a female of the same racial mixture.

An enormous mass of material, statistics, tables and curves may be gathered from the literature on blood pressure readings, but it is very difficult to correlate the readings from different observers and to arrive at any definite standard for comparison. In fact, standards of normal seem to vary considerably in various parts of the world, dependent on certain environmental influences, and what would be a distinct hypotension in one locality would not be considered so in another.

Method of Collecting the Data. A Tycos sphygmomanometer of the spring type was used with a standard 12-cm. wide arm band. This was checked against a mercury column before and after the data were secured and a small corrective figure added. Practically all the readings were taken by one observer, with the patient in each case seated in a chair with the arm about on a level with the heart. Some of the patients were perfectly healthy individuals, while most of them had a variety of complaints. They represent the sick as well as the healthy. The systolic reading was taken at the appearance of the first sound, and the diastolic at the change in tone.

Observations. Readings were reported on 1066 Mayas and Mestizos, aged 15 years and over. These figures are massed and grouped in Table 1. Table 2 gives the blood pressure distribution by pressures for both races and sexes.

TABLE 1.—AVERAGES OF SYSTOLIC, DIASTOLIC AND PULSE PRESSURES ON MAYAS AND MESTIZOS OF BOTH SEXES OVER 15 YEARS OF AGE. BASED ON 1066 CASES.

Ages.	15 to 19.	20 to 29.	30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	80 to 89.
Average systolic	112.0	112.4	119.4	122.5	130.7	132.6	132.1	132.3
Average diastolic	70.2	71.7	75.6	75.0	75.3	73.3	70.0	78.4
Average pulse	41.8	40.7	43.8	47.5	55.4	59.3	61.3	53.9
Number of cases	122	292	257	184	123	61	24	3

Consolidated Averages for All Ages.

	Both sexes.	Males.	Females.
Systolic	119.9	115.7	123.3
Diastolic	73.5	71.5	74.8
Pulse	46.4	44.2	47.5

It will be seen that in the consolidated group 68.4 per cent of all readings fall between 100 and 130 mm. of mercury, and that in the same range there were 59.6 per cent of the male Mayas, 69.7 per cent of the female Mayas; 66.5 per cent of the Mestizos and 72 per cent of the Mestizas.

Regarding 150 mm. as the upper limit of normal systolic pres-

sure, it will be seen that there were 6 per cent above this limit in the entire group. Within this group were: Maya males, 3.5 per cent; Maya females, 8 per cent; Mestizos, 2.8 per cent; Mestizas, 7.3 per cent.

TABLE 2.—DISTRIBUTION OF SYSTOLIC BLOOD PRESSURES OF MAYAS AND MESTIZOS OF BOTH SEXES OF OVER 15 YEARS OF AGE. BASED ON 1066 CASES.

Pressures.	70 to 79.	80 to 89.	90 to 99.	100 to 109.	110 to 119.	120 to 129.	130 to 139.	140 to 149.	150 to 159.	Over 160.
Number of cases	6	22	72	212	279	237	106	68	32	32
Per cent of total	0.6	2.1	6.7	19.9	26.2	22.3	9.9	6.2	3.0	3.0
Distribution of Systolic Pressures for Maya Males: 143 Cases.										
Number of cases	3	10	17	32	29	24	17	6	2	3
Per cent of group	2.1	7.0	11.8	22.5	20.4	16.7	11.8	4.2	1.4	2.1
Distribution of Systolic Pressures for Maya Females: 335 Cases.										
Number of cases	0	1	19	71	95	67	28	27	17	10
Per cent of group	0	0.3	5.6	21.3	28.4	20.0	8.4	8.0	5.1	2.9
Distribution of Systolic Pressures for Mestizos (Males): 245 Cases.										
Number of cases	3	10	23	53	55	55	26	13	1	6
Per cent of group	1.2	4.1	9.4	21.7	22.4	22.4	10.7	5.3	0.4	2.4
Distribution of Systolic Pressures for Mestizas (Females): 343 Cases.										
Number of cases	0	1	13	56	100	91	35	22	12	13
Per cent of group	0	0.3	3.8	16.3	29.2	26.5	10.2	6.4	3.5	3.8

Thus, the female systolic pressures average several points higher than those for males. There are more females in the abnormally high pressure groups and more males having systolic pressure below 100 mm. In these low groups were 20 per cent of Maya males and only 5.9 per cent of Maya females; 14.7 per cent of Mestizos and only 4.1 per cent of Mestizas.

Comparison With Standards Elsewhere. Tables of blood pressure figures are of value only in comparison with blood pressure figures which may be considered as a standard. Certain observations may be quoted from North America to give a temperate zone standard, and others from various places to give a tropical zone and Oriental standard.

Woley has given the variation of systolic blood pressure in 1000 cases in the United States. His average for males was 127.5 mm. and for females 120 mm. His readings were taken by palpation which would make them 3 to 5 points lower than if taken by auscultation.

Norris quotes a table of blood pressure averages made by Dr. J. W. Fisher of the Northwestern Mutual Life Insurance Company, in which the averages are given for 64,574 presumably healthy adults. The systolic average was 123.2, diastolic 80 and pulse pressure 43.2.

Symonds gives the blood pressure findings in 150,419 males,

accepted life insurance risks and in 11,937 females, accepted life insurance risks. His average for males of all ages was 127.6 mm. systolic; 83.5 mm. diastolic and pulse 44.1 mm.

Alvarez gives the average figures for 14,934 men and women students of all ages, 16 to 40 years. The men average 128.9 mm. systolic and the women 117.3 mm. systolic. These represent a rather highly specialized social group and it is questionable whether the figures could be considered as standards for a population as a whole.

Barach and Marks give the blood pressure distribution figures in 742 adult males between 15 and 30 years of age. The table of figures follows later.

Donnison has given the blood pressure findings in 1000 East African natives. His table of figures will appear later.

Hudson and Young have shown the distribution of systolic blood pressures in 1056 Arabians.

Ashford and Dowling have analyzed the blood pressure findings in 250 patients in Puerto Rico, and determined the average systolic pressure for males as 114.3 mm. and for females 120.1 mm.

Torgerson has recorded the blood pressure findings in 100 consecutive hospital patients in Puerto Rico. The average systolic pressure was 120.2 mm., diastolic 73.8 mm. and pulse pressure 46.4 mm.

Chamberlain has presented the averages of blood pressures of American soldiers living in the Philippines as 115 mm. systolic for 18 to 30 years of age, and 118 mm. systolic for over 30 years of age.

Foster made a record of blood pressures of foreigners and Chinese in China. His figures will be given later.

An attempt will be made to correlate the observations of these various authors and to compare them with our observations made in Yucatan. The easiest way to do this will be to group the figures from various places in tabular form.

TABLE 3.—AVERAGE SYSTOLIC BLOOD PRESSURE ACCORDING TO VARIOUS AUTHORS.

Author.	Place.	Ages.	Sex.	Race.	No. of cases.	Systolic.	Diastolic.	Pulse.
Woley	U. S.	15–60	M	Amer.	1,000	127.5		
			F	"	....	120.0		
Norris	U. S.	15–60	Both	"	64,574	123.2	80.0	43.2
Symonds	U. S.	15–	M	"	150,419	127.6	83.5	44.1
Alvarez	U. S.	16–40	M	"	6,000	128.9		
			F	"	8,934	117.3		
Ashford	Puerto Rico	15–	M	P. R.	250	114.3		
			F	"	....	120.1		
Torgerson	" "	All	Both	"	100	120.2	73.8	46.4
Chamberlain	Philippines	18–30	M	Amer.	1,000	115.0		
		over 30	M	"	....	118.0		
Saunders	Yucatan	15–	Both	Yucatecan	1,066	119.9	73.5	46.4

Table 3 groups some of the consolidated averages from various authors. It shows the average for the Yucatecans to be from 4 to 8 points lower than the averages from the United States. Table 4 compares averages by age groups. This table of figures indicates that in the lower age groups the average Yucatecan systolic pressures are appreciably lower than those given for the United States. In the age groups above 50 years, however, the Yucatecan pressures tend to equal the figures from one source.

TABLE 4.—AVERAGE SYSTOLIC BLOOD PRESSURES BY AGE GROUPS: VARIOUS AUTHORS.

Age groups.	1.	2.	3.	4.	5.	6.	7.
15 to 19	...	123.5	117.1	123.1	107.0	...	112.0
20 to 24	122	124.2	120.5	122.8			
25 to 29	...	124.5	121.6	126.4	110.1	115.0	112.4
30 to 34	...	125.1	122.1	126.1			
35 to 39	127	125.3	122.8	125.5	114.5	118.0	119.4
40 to 44	...	126.4	124.1	118.3			
45 to 49	130	128.2	125.5	113.2	119.5	...	122.5
50 to 54	...	130.2	127.7	109.8			
55 to 59	132	133.5	130.3	106.6	124.8	...	130.7
60 to 64	138	135.2	132.5	105.8	121.4		
65 to 69	...	...	...	...	...	...	132.7
70 to 74							
75 to 79	...	...	...	...	...	...	132.1
80 to 84							
85 to 89	...	...	...	...	...	...	132.3

1. Woley's figures for 1000 Americans.
2. Symonds' figures for 150,000 American males (last figure for ages 60 and over).
3. Norris-Fisher's figures for 64,000 Americans (age groups 16 to 17, 18 to 22, 23 to 27, etc.).
4. Donnison's figures for 1000 East African natives (last figure for age 60 and over).
5. Ashford's figures for 250 Puerto Ricans (last figure for age 60 and over).
6. Chamberlain's figures for 1000 Americans in Philippines (ages 18 to 30 and over 30).
7. Saunders' figures for 1066 Yucatecans.

The high pressures in the upper age groups in Yucatan come chiefly from cases of hypertension among the females, as shown in the distributional Table 2. It is usually stated that blood pressures for females average considerably lower than for males. Alvarez shows that in his observations on college students the systolic pressures for women average considerably lower than for men. He says: "In young women there seems to be a high degree of correlation between the incidence of hypertension and the presence of various signs and symptoms of ovarian hypofunction." He ascribes hypertension not to infections or to strenuous life but to an inherited peculiarity, the appearance of which can be suppressed in women so long as the ovaries function well. Norris, in commenting on the sexual differences in blood pressure, noted that females average lower up to 40 years when the average systolic pressure for women is 1 or 2 mm. less than for men up to the age of 40 years, and that after 40 years the systolic pressures of women are quite equal to those of men and may be even higher.

The idea of ovarian hypofunction having a relationship to increased arterial pressure might have a bearing on the higher blood pressure of the Yucatecan women as compared with men. This difference was especially manifest after 40 years of age. Menstrual disorders, too, occurred among the Yucatecan women much more frequently than one would expect, and it may be that many of these disorders of menstruation were based on an underlying ovarian hypofunction.

Table 5 shows systolic blood pressure distributions from various sources. For Americans in the United States the greatest number of systolic pressures are found in the 120 to 129 mm. group and about 71 per cent are between 110 and 140 mm. My figures for Yucatecans show the largest number in the 110 to 119 mm. group, and about 68 per cent falling between 100 and 129 mm. This further substantiates the idea already brought out that the general average of systolic pressures is lower among the Mayas and Yucatecans generally than among North Americans. Hudson and Young's figures for Arabians show, however, the peak at the 100 to 109 mm. level with 68 per cent of the cases falling between 90 and 120 mm., or about 10 points lower than the Yucatecans. Foster's figures, too, show that for foreigners in China and Chinese in China the peak is at the 100 to 109 mm. level, with 72 per cent of the foreigners and 79 per cent of the Chinese falling between 90 and 120 mm. levels.

TABLE 5.—DISTRIBUTION PERCENTAGES OF SYSTOLIC BLOOD PRESSURES: VARIOUS AUTHORS.

Systolic pressure.	1.	2.	3a.	3b.	4.
70 to 79	0.0	0.5	0.0	0.0	0.6
80 to 89	0.0	4.2	2.0	3.0	2.1
90 to 99	1.1	18.0	19.0	18.0	6.7
100 to 109	3.5	27.0	30.0	32.0	19.9
110 to 119	16.7	23.0	23.0	29.0	26.2
120 to 129	31.2	14.0	15.0	10.0	22.3
130 to 139	23.3	8.0	5.0	3.0	9.9
140 to 149	14.5	3.0	3.0	3.0	6.3
150 to 159	6.8	1.2	1.0	2.0	3.0
160 to 169	2.1	1.6	2.0	1.0	1.5
170 to 179	0.4	0.0	0.0	0.0	1.5

1. Marks, B. G.: Blood pressure in 656 adult male Americans.
2. Hudson and Young: Blood pressure in 1056 Arabians.
3a. Foster: Blood pressure in 120 foreigners in China.
3b. Foster: Blood pressure in 273 Chinese in China.
4. Saunders, G. M.: Blood pressure in 1066 Yucatecans.

It has been made clear that systolic blood pressure averages for Yucatecans range lower than systolic pressures in the United States, and slightly higher than in certain other places in the tropics or in China. It has been variously stated that in a tropical climate blood pressures range lower than in a temperate or cold climate, and practically all observations have tended to bear out the truth of this assertion. Ashford and Dowling's figures show a lower average for 250 Puerto Ricans. Torgerson's figures show a slightly lower average for 100 Puerto Ricans; Donnison's figures for African

natives show a lower average; Hudson and Young's figures for Arabians show a lower average, and Fleming states that the average systolic pressure of Americans living in the Philippines is 10 mm. less than the average of those in the temperate zone. Although he says "the blood pressures of Americans living in the Philippines differs little, if any, from the average at home." Chamberlain gives the figures for Americans in the Philippines as: systolic pressure average 115 mm. for 18 to 30 years of age, and 118 mm. for over 30 years of age. By referring to Table 3 these averages are seen to be distinctly lower than those of Woley, Norris, Symonds and Alvarez for Americans living at home. Roddis and Cooper studied the blood pressures of 173 American naval officers temporarily resident in the tropics, and stated that the systolic pressures averaged 11.5 points and the diastolic 11.2 points lower than the standard for the temperate zone, and that the average systolic pressure of 16 of those studied increased 9 points within a month after returning to the temperate zone.

It would appear, then, that in the tropics systolic pressures average lower than in temperate zones, though whether by virtue of climate or other environmental factors is not clear.

The observations from China showing low systolic pressure averages would tend to indicate that other than climatic influences are at work, for China is not a tropical country. Foster has stated that the blood pressure of a series of Occidentals living in China showed that the average for foreigners was about the same as that of the local Chinese, and that the blood pressures of the majority of the persons studied were lower in China than in America. Tung, in discussing the relative hypotension of foreigners in China, showed that 58 Americans, after residing 1 year in China, had a systolic pressure average of 9 points lower and a diastolic pressure average of 11 points lower than previously. He says that "the perpetual rush, tension and excitement that characterizes American life, and the comparatively slower and calmer life in Peking, although the work here may be no less strenuous, may be important factors in the causation of the relative hypotension."

Cadbury concluded from his studies that the blood pressures of Cantonese students from two of the southern provinces of China were lower than blood pressures of a corresponding group of Americans and Europeans of the same age, height and weight.

The reason for the lower systolic pressures among the Yucatecans is not clear. The warm climate probably plays an important part. Dally states that "in temperate climates a continued spell of warm weather frequently results in reducing the maximal pressure by 10 to 20 mm.; the contrary effect being produced by cold."

Fleming explains the lower systolic pressures of Americans in the Philippines as due to decreased peripheral resistance to circulation due to climatic factors. Roddis and Cooper ascribe these

lower systolic findings to climatic influences. The slower, more placid life in Yucatan is probably contributory. Foster, discussing lower pressures in China, feels that there may be a subconscious adjustment to the unhurried life of the East that lowers general tone. The life in Yucatan is certainly unhurried when compared with that in North America or Europe.

The height and weight of the Yucatecans may have some bearing on the lower blood pressures. Williams has shown that Yucatecans have lower height and weight standards than Americans and Europeans, and Symonds has demonstrated that blood pressures increase with height and weight. The women of Yucatan are generally more obese than the men and seem to have higher blood pressures.

The common occurrence of low grades of anemia among the Yucatecans probably does not influence the blood pressure. Norris states that "blood pressure bears no constant relation either to the percentage of hemoglobin or to the total number of corpuscles." Torgerson has shown that anemia does not appear to influence the blood pressure in Puerto Rico.

The occurrence of infections of various kinds may play some part in lowering the blood pressure of Yucatecans. Malaria cannot be a very important factor in Yucatan because its incidence there is low, but on the other hand the average systolic pressure in 28 persons whose blood showed plasmodia was only 104.6 mm., as compared with 119.9 mm. for the whole group of cases. Norris says that in chronic malaria hypotension is the rule.

Ascariasis is very common in Yucatan, probably 80 per cent of the population being infested. Dally states that "by reason of intestinal disturbances produced by these parasites (ascaris) the general health becomes impaired, and low arterial pressure often results."

But, whatever the other reasons may be, the slightly lower blood pressures prevailing among Yucatecans as compared with North Americans at home are probably due chiefly to two factors: the tropical climate and the unhurried life of the people.

The attention here has been devoted chiefly to systolic pressures. For the sake of brevity, the tables of diastolic and pulse pressures were not included here, but it may be stated that the diastolic pressures of Yucatecans is constantly lower than standards from North America, and that pulse pressures range about the same.

Summary. 1. Systolic blood pressures on Mayas and Mestizos seem to range 4 to 8 points below normal standards for blood pressures in the United States of America.

2. Female systolic pressures averaged higher than those of the males.

3. Diastolic pressures also ranged lower than in the United States of America.

4. Systolic blood pressures were grouped chiefly about the 110 to 119 mm. level among the Yucatecans, as against the 120 to 129 mm. level for pressure in the United States of America.

5. Some interesting differences for age groups were also indicated by the figures.

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DIAGNOSTIC IMPORTANCE OF BILIARY CRYSTALS.*

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The presence of cholesterol crystals in the duodenal contents of a patient with cholecystitis was first noted by Einhorn.[1] Since then, various investigators[2–11] have reported the finding of cholesterol crystals or calcium bilirubinate pigment or both in preoperative specimens of bile, in cases of cholecystitis with and without stones. Nevertheless, bile microscopy has not been employed as frequently as it should be, especially in those patients with a history of gastric symptoms and in whom a diagnosis of gall bladder disease cannot be definitely established by the standard methods of examination.

It was thought of interest to study the diagnostic value of the microscopic examination of preoperative specimens of bile in a group of proved cases of calculous and non-calculous cholecystitis.

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While in many of these patients the history pointed to gall bladder disease, in some the symptoms did not indicate gall bladder pathology. Included in this series were also cases in which bile microscopy was the only means by which a diagnosis of gall tract disease could be established. This study was made with the aid of photomicrographs of biliary crystals, taken before cholecystectomy, and compared with photomicrographs of crystals from postoperative specimens of bile and scrapings of stones removed from the gall bladder.

Cholesterol crystals and calcium bilirubinate pigment are the crystalline elements most commonly found in the bile preoperatively in cases of gall bladder disease. Other types of biliary crystals are encountered less frequently.

Typical cholesterol crystals are very characteristic and easily recognizable, although occasionally it may be necessary to differentiate them from amino-acid crystals.[12] Atypical cholesterol crystals have also been observed in the duodenal contents,[7] although their diagnostic significance has never been emphasized. These crystals are colorless and assume various forms, some even having the window pane shape of typical cholesterol crystals, but without the characteristic broken corner. The chemical composition of atypical cholesterol crystals has not been fully established. This subject is still under investigation.

Calcium bilirubinate pigment, sometimes termed "calcium bilirubinate crystals," should be grouped into two classes: (1) The brick red or dark brown amorphous masses; (2) the light brown or amber colored granules. Hereafter, the former will be referred to as the amorphous type, and the latter as the granular type of calcium bilirubinate pigment.

Calcium carbonate crystals were also observed in the bile preoperatively in 2 of our cases of cholelithiasis. These crystals were colorless, oblong in shape and were soluble in hydrochloric acid. In 1 patient (Case 3) the crystals were found after operation in the scrapings of the whitish elevated areas, on the outer surface of a cholesterol and calcium bilirubinate gall stone. In the other patient the calcium carbonate crystals were observed postoperatively, in the "white bile" which was removed from the gall bladder.

The method of procedure employed in examining the bile of our patients was as follows: The duodenal tube was passed, preferably, in the evening. On the following morning the fasting specimen of bile and the specimens obtained after the instillation of 2 ounces of a 25 per cent solution of magnesium sulphate, or 5 per cent solution of peptone, were collected and examined. Biliary crystals were usually present in the grayish, dark brown or brick red flakes found in the bile. It was not necessary to centrifuge the specimens of bile in order to obtain the crystals. No special significance was attached to the A, B, and C fractions of the bile, since biliary

crystals were found as frequently in the fasting specimen of duodenal contents as in the specimens obtained after the instillation of magnesium sulphate or peptone. Furthermore, crystalline elements were seen, preoperatively, in specimens of bile, even when "B" bile was not obtained, although the cystic duct was patent.

The blood cholesterol (Bernhard-Drekter method[13]) and the icterus index (Maue-Bernhard method[14]) were determined in all patients.

Sixty-nine of the patients in whom biliary crystals were found in preoperative specimens of bile came to operation. In 63 cases (91.3 per cent) cholelithiasis (including patients with choledocholithiasis) or cholecystitis without stones was found. The types of crystals and pigment which were present in the bile preoperatively in these 63 patients were similar to the crystalline elements observed in the scrapings of the calculi or the bile removed from the gall bladder, at the time of operation. In the remaining 6 patients (8.7 per cent of the series) no stones were found at operation, nor did the gall bladder appear macroscopically diseased.

The 69 patients operated upon were grouped as follows:

1. Forty-seven patients in whom the history was typical of gall bladder disease.

2. Twenty-two patients in whom the history of gastric symptoms did not point to gall bladder disease.

GROUP I. Specimens of bile, which were obtained before operation from the 47 cases in this group, revealed the following (Table 1): Numerous cholesterol crystals with little or no calcium bilirubinate pigment were found in 9 patients (19.1 per cent); a large amount of calcium bilirubinate pigment with few or no cholesterol crystals was present in 8 patients (17 per cent); numerous cholesterol crystals and an abundance of calcium bilirubinate pigment were found, in the same bile, in the remaining 30 patients (63.9 per cent). In 2 of these patients calcium carbonate crystals were also found. Cholecystography (oral method), as can be seen from Table 2, showed roentgenographic evidence of calculi or pathologic gall bladder in 39 (82.9 per cent) of the 47 patients in Group I. Normal cholecystograms were seen in the remaining 8 patients (17.1 per cent). At operation, cholelithiasis was found in 39 patients (83 per cent); cholecystitis without stones in 5 patients (10.7 per cent), and in 3 patients (6.3 per cent) no calculi were found, nor did the gall bladder appear grossly diseased.

GROUP II. Sixteen of 22 patients of this group complained of various gastric symptoms, with little or no abdominal pain. Preoperative specimens of bile in these 16 cases revealed cholesterol crystals, with little or no calcium bilirubinate pigment, in 4 patients (25 per cent); a large amount of calcium bilirubinate pigment, with few or no cholesterol crystals, in 4 patients (25 per cent); and numerous cholesterol crystals and an abundance of calcium bilirubinate pigment, in the same bile, in the other 8 patients (50 per cent).

TABLE 1.—PREOPERATIVE FINDINGS IN THE BILE OF 69 PATIENTS COMING TO OPERATION.

		No. of patients.	Per cent.	Findings in preoperative specimens of bile.
Group I: 47 patients in whom the history was typical of gall bladder disease		9	19.1	Numerous cholesterol crystals with little or no calcium bilirubinate pigment.
		8	17.0	Large amount of calcium bilirubinate pigment with few or no cholesterol crystals.
		30	63.9	Numerous cholesterol crystals and large amount of calcium bilirubinate pigment in the same bile; in 2 of these patients, calcium carbonate crystals were also present.
Group II: 22 patients in whom the history of gastric symptoms did not point to gall bladder disease	16 patients who complained of gastric symptoms with little or no pain	4	25.0	Numerous cholesterol crystals with little or no calcium bilirubinate pigment.
		4	25.0	Large amount of calcium bilirubinate pigment with few or no cholesterol crystals.
		8	50.0	Numerous cholesterol crystals and large amount of calcium bilirubinate pigment in the same bile.
	6 patients with a history and radiographic evidence of penetrating duodenal ulcer	1	16.7	Numerous cholesterol crystals with no calcium bilirubinate pigment.
		3	50.0	Large amount of calcium bilirubinate pigment with few or no cholesterol crystals.
		2	33.3	Numerous cholesterol crystals and large amount of calcium bilirubinate pigment in the same bile.

NOTE.—"Cholesterol crystals" refers to typical and atypical cholesterol crystals. "Calcium bilirubinate pigment" refers to amorphous and granular types of calcium bilirubinate pigment.

TABLE 2.—FINDINGS AT OPERATION.

Biliary crystals were present in the following.	Cholecystography (oral method). Roentgenographic evidence of calculi or pathologic gall bladder (including "no gall bladder shadow").	Normal functioning gall bladder shadow.	Operative findings.	
Group I: 47 patients in whom the history was typical of gall bladder disease	39 patients (82.9%)	8 patients (17.1%)	Cholelithiasis, 39 patients (83%) Cholecystitis without stones, 5 patients (10.7%)	44 patients (93.7%) with calculous or non-calculous cholecystitis.
			No calculi or macroscopic evidence of cholecystitis	3 patients (6.3%).
Group II: 22 patients in whom the history of gastric symptoms did not point to gall bladder disease	17 patients (77.2%)	5 patients 22.8%)	Cholelithiasis, 12 patients (54.5%) Cholecystitis without stones, 7 patients (31.8%)	19 patients (86.3%) with calculous or non-calculous cholecystitis.
			No calculi or macroscopic evidence of cholecystitis	3 patients (13.7%).

The remaining 6 patients of Group II gave an ulcer history and also presented roentgenographic evidence of a penetrating duodenal ulcer. The bile showed preoperatively numerous cholesterol crystals in 1 patient (16.7 per cent); a large amount of calcium bili-

rubinate pigment with few or no cholesterol crystals in 3 patients (50 per cent); and numerous cholesterol crystals and an abundance of calcium bilirubinate pigment, in the same bile, in the last 2 patients (33.3 per cent).

Roentgenographic examination of the gall bladder by the Graham method (oral) of the 22 patients in Group II revealed evidence of calculi or pathologic gall bladder in 17 patients (77.2 per cent). Normal cholecystograms were seen in the remaining 5 patients (22.8 per cent). At operation cholelithiasis was found in 12 patients (54.5 per cent) and non-calculous cholecystitis was present in 7 patients (31.8 per cent). In 3 patients (13.7 per cent) of this group, no calculi were found, nor was the gall bladder macroscopically diseased.

The amorphous type of calcium bilirubinate pigment, or "calcium bilirubin crystals," was seen more consistently in patients with stones than in non-calculous cholecystitis. The granular type of calcium bilirubinate pigment, or bunch-berry crystals, was seen with equal frequency in the bile sediment before operation in patients with calculi or in those patients with cholecystitis without stones.

A point that must be borne in mind is that, at times, a non-calculous cholecystitis may be found at operation in addition to a dilated common duct. The fact that no stones are found does not eliminate the possibility that a stone was present, and was passed.

The various forms of crystals, in the different types of patients under observation in this series, are illustrated by the accompanying photomicrographs and case reports.

The blood cholesterol and icterus index were likewise determined before operation in all patients. In 37 of the 69 patients (53.5 per cent) hypercholesteremia was present. The blood cholesterol varied in these patients from 201 mg. to 408 mg. per 100 cc. of serum. Latent jaundice was found in 41 of the 69 patients (59.4 per cent) at some time during the period of observation. In patients with biliary colic, as was pointed out in a previous paper,[15] the blood for the icterus index should be drawn as soon as possible after the onset of the pain.

Comment. In order to emphasize the diagnostic importance of bile microscopy, photomicrographs of biliary crystals in preoperative specimens of bile were compared with photomicrographs of crystals obtained from the scrapings of calculi or from bile removed from the gall bladder at operation. Typical and atypical cholesterol crystals, granular and amorphous types of calcium bilirubinate pigment and calcium carbonate crystals, which were observed preoperatively in the bile, were found to be similar to the crystals present in stones or in the bile removed at operation.

In evaluating the diagnostic importance of the crystalline elements in preoperative specimens of bile, one point should always be borne in mind, namely, the number of crystals seen and the

amount of pigment observed in the bile. A few scattered crystals or a small amount of calcium bilirubinate pigment, occurring separately or together, has not much diagnostic significance. But numerous cholesterol crystals and a large amount of calcium bilirubinate pigment, separately or collectively, in the bile preoperatively does indicate in most patients a calculous or non-calculous cholecystitis. The proper interpretation of bile microscopy may be the only means of definitely establishing the diagnosis of gall tract disease. This has been illustrated in some of the case reports.

Although bile microscopy was of invaluable aid in our gall bladder cases, it was not always possible, by crystal morphology, to differentiate between calculous and non-calculous cholecystitis (Table 3). Of the 14 patients in whom cholesterol crystals with little or no calcium bilirubinate pigment were found in preoperative specimens of bile, cholelithiasis was present in 9 patients (64.3 per cent), cholecystitis without stones in 3 patients (21.4 per cent), and in 2 patients (14.3 per cent) no calculi or macroscopic evidence of cholecystitis were found. Of the 15 patients in whom calcium bilirubinate pigment crystals with little or no cholesterol crystals were seen in the bile before operation, cholelithiasis was found in 7 patients (46.7 per cent), non-calculous cholecystitis in 5 patients (33.3 per cent), and in 3 patients (20 per cent) no stones nor gross evidence of cholecystitis was found. Of the 40 patients in whom numerous cholesterol crystals and a large amount of calcium bilirubinate pigment were observed in the same bile preoperatively, cholelithiasis was present in 35 patients (87.5 per cent), cholecystitis without stones in 4 patients (10 per cent), and in 1 patient (2.5 per cent) no calculi nor macroscopic evidence of cholecystitis was found. In 2 of the patients with cholelithiasis calcium carbonate crystals were also present.

TABLE 3.—COMPARISON OF THE CRYSTAL MORPHOLOGY WITH THE OPERATIVE FINDINGS.

Cases.	Per cent.	Crystalline elements in preoperative specimens of bile.	Operative findings.	
14	20.3	Numerous cholesterol with little or no calcium bilirubinate pigment	Cholelithiasis, 9 patients (64.3%) Cholecystitis without stones, 3 patients (21.4%)	12 patients (85.7%) calculous or non-calculous cholecystitis
			No calculi or macroscopic evidence of cholecystitis, 2 patients (14.3%)	
15	21.8	Large amount of calcium bilirubinate pigment with few or no cholesterol crystals	Cholelithiasis, 7 patients (46.7%) Cholecystitis without stones, 5 patients (33.3%)	12 patients (80%) calculous or non-calculous cholecystitis
			No calculi or macroscopic evidence of cholecystitis, 3 patients (20%)	
40	57.9	Numerous cholesterol crystals and large amount of calcium bilirubinate pigment together	*Cholelithiasis, 35 patients (87.5%) Cholecystitis without stones, 4 patients (10%)	39 patients (97.5%) calculous or non-calculous cholecystitis
			No calculi or macroscopic evidence of cholecystitis, 1 patient (2.5%)	

* In 2 of these patients calcium carbonate crystals were also present in preoperative specimens of bile.

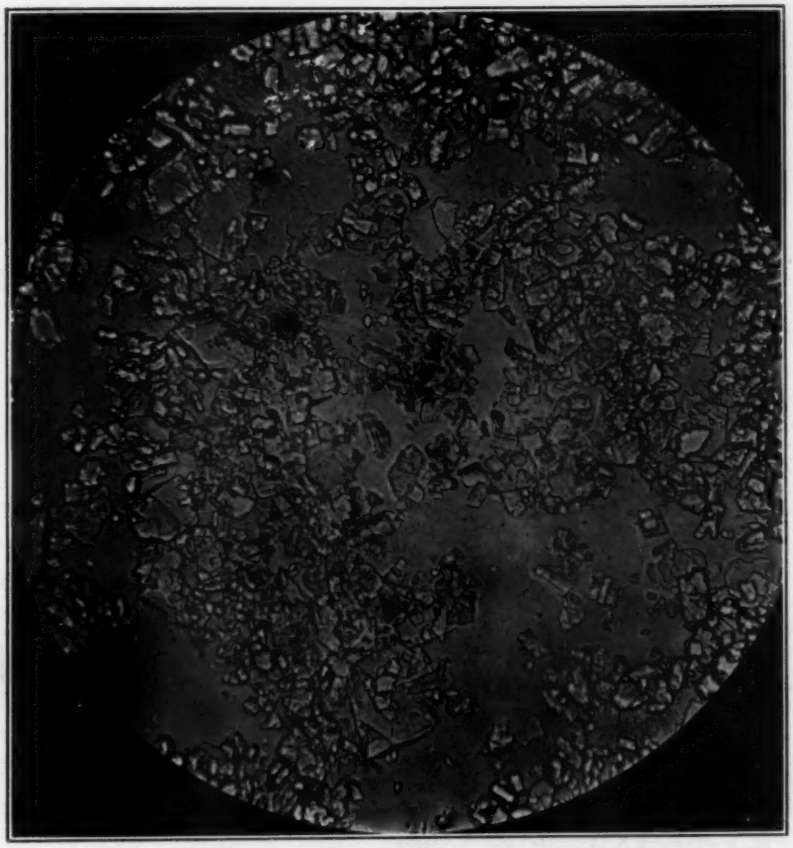

FIG. 1.—Patient S. A. Typical cholesterol crystals (preoperative specimen of bile).

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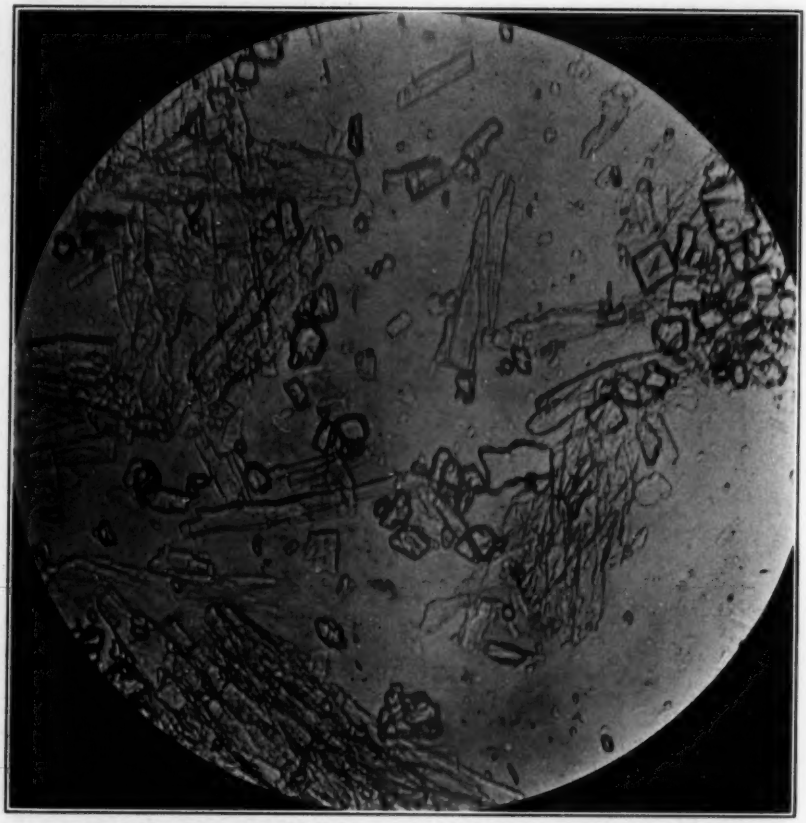

FIG. 2.—Patient S. A. Atypical cholesterol crystals (preoperative specimen of bile).

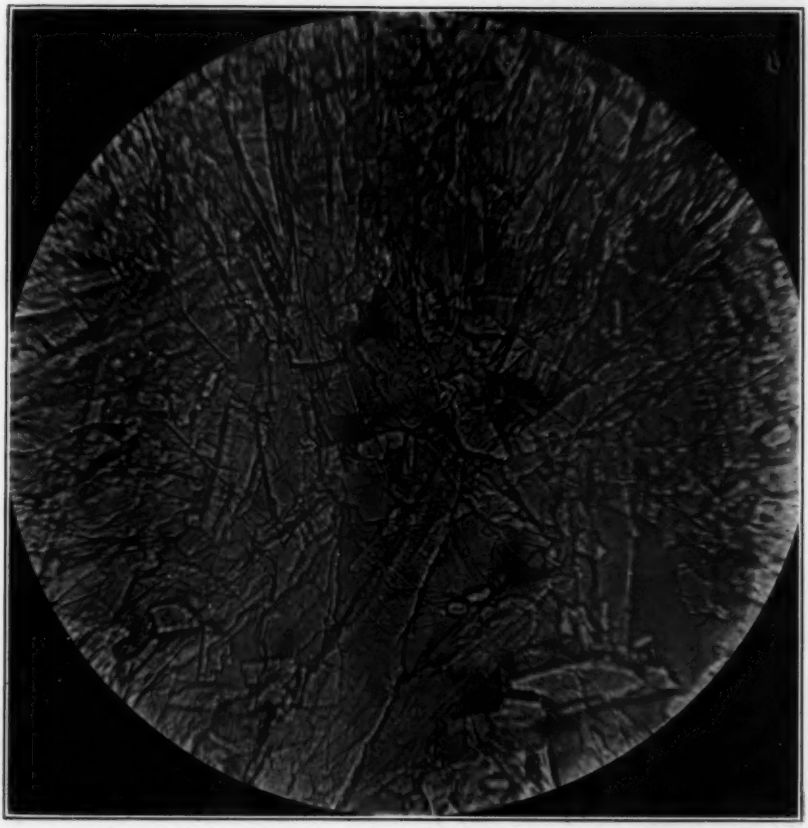

FIG. 3.—Patient S. A. Typical and atypical cholesterol crystals (scrapings of stone removed from gall bladder).

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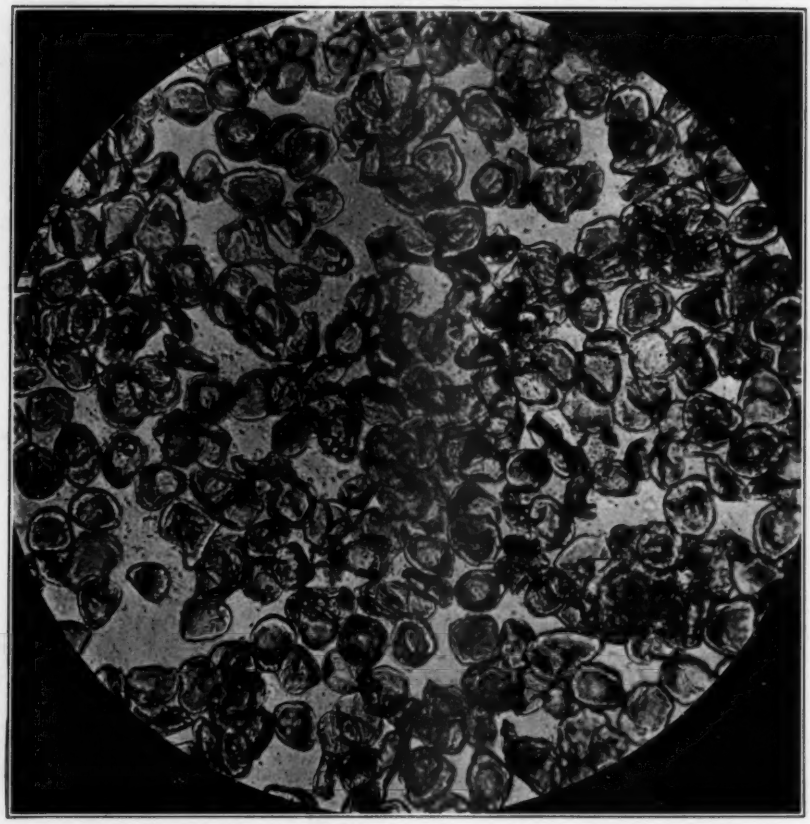

FIG. 4.—Patient Mrs. R. B. Calcium bilirubinate pigment—granular type (preoperative specimen of bile).

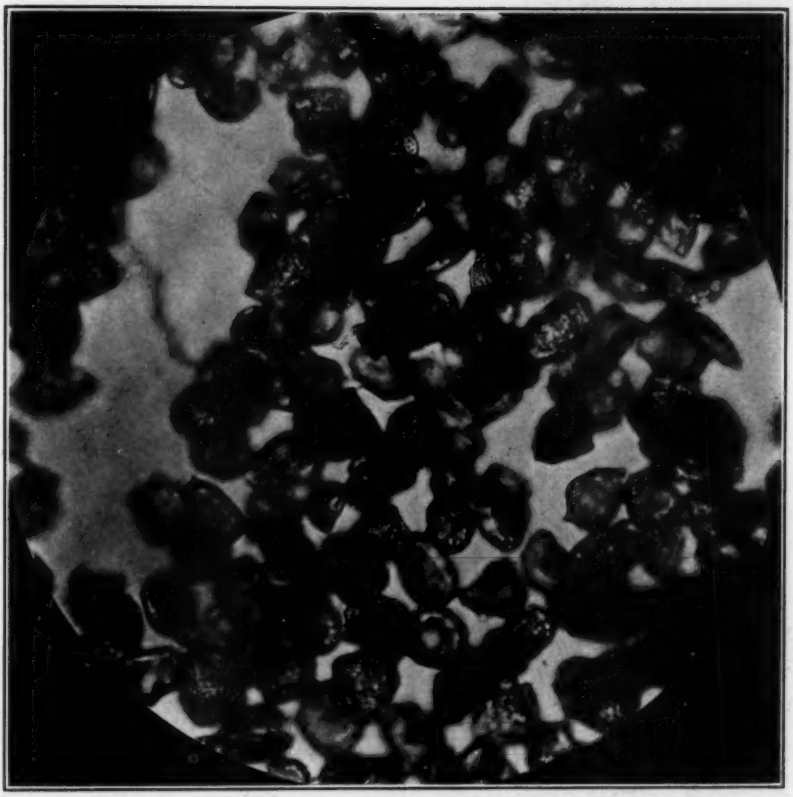

FIG. 5.—Patient Mrs. R. B. Calcium bilirubinate pigment—granular type (scrapings of stone from gall bladder).

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FIG. 6.—Patient B. G. Calcium carbonate crystals (scrapings from whitish elevated area of gall stone).

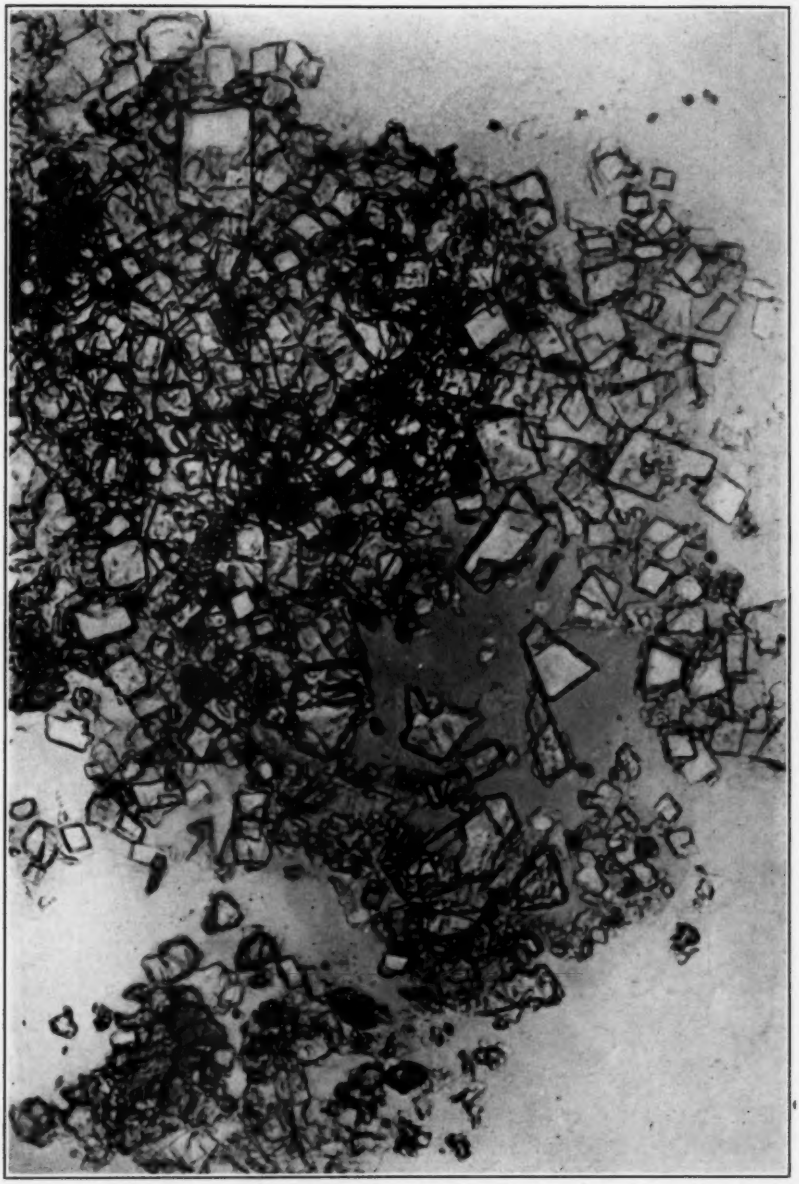

FIG. 7.—Patient N. S. Typical cholesterol crystals and amorphous calcium bilirubinate pigment in the same particle (preoperative specimen of bile).

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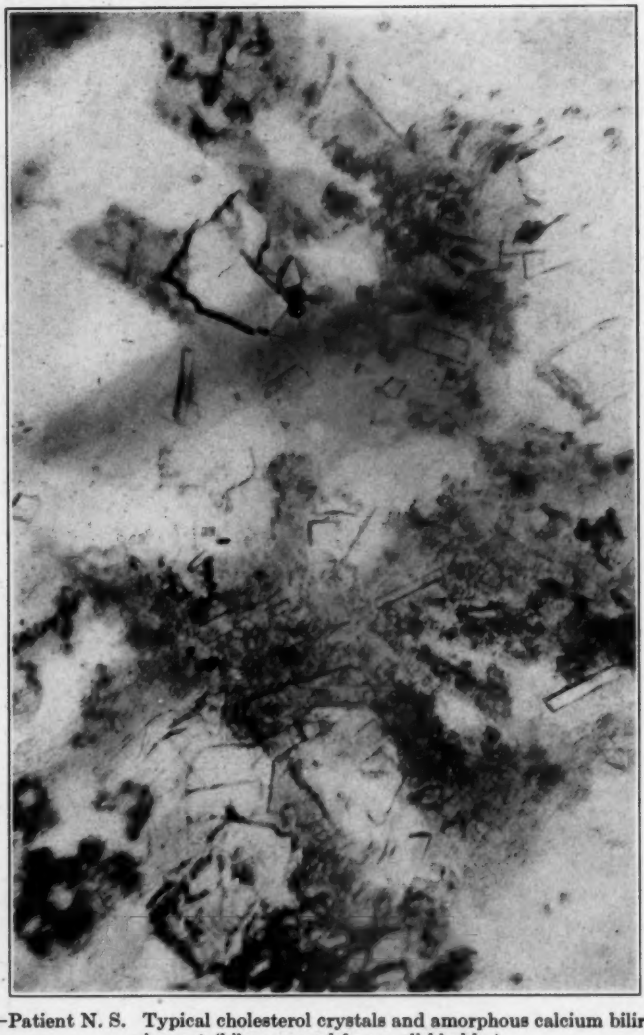

FIG. 8.—Patient N. S. Typical cholesterol crystals and amorphous calcium bilirubinate pigment (bile removed from gall bladder).

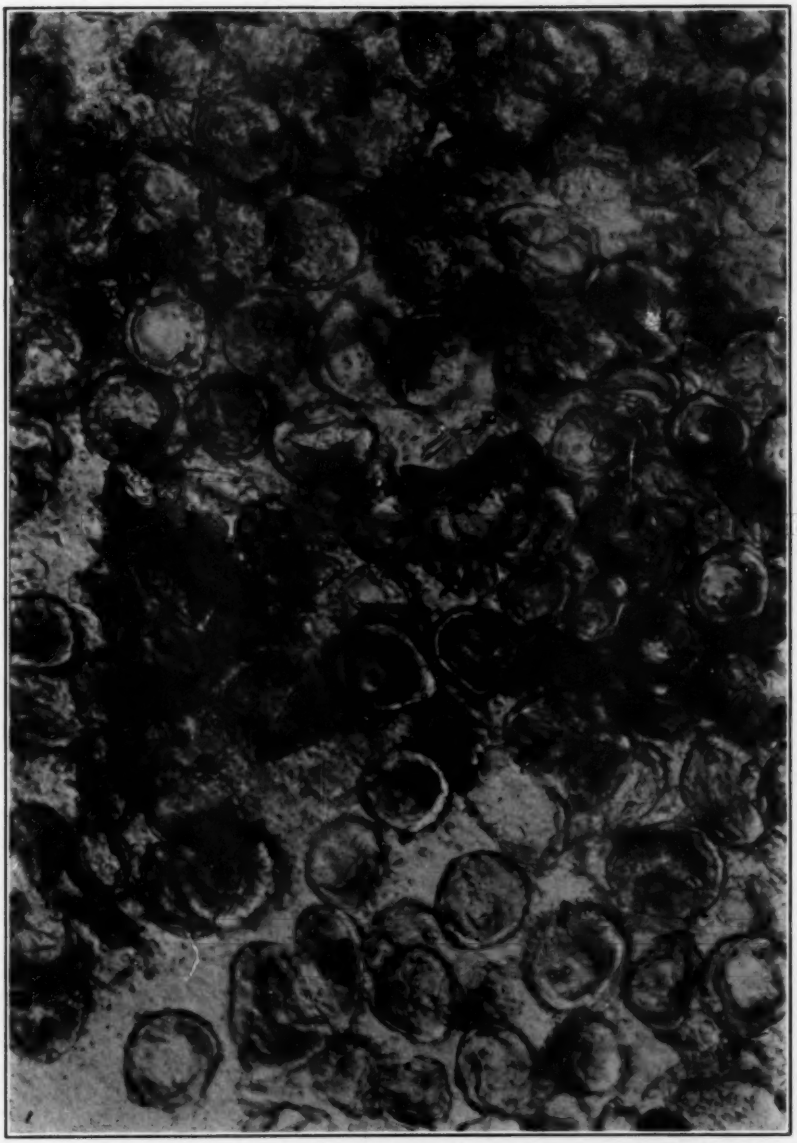

FIG. 9.—Patient Mrs. M. D. Calcium bilirubinate pigment—granular and amorphous types with the former predominating (preoperative specimen of bile).

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FIG. 10.—Patient Mrs. M. D. Calcium bilirubinate pigment—amorphous and granular types (bile removed from gall bladder).

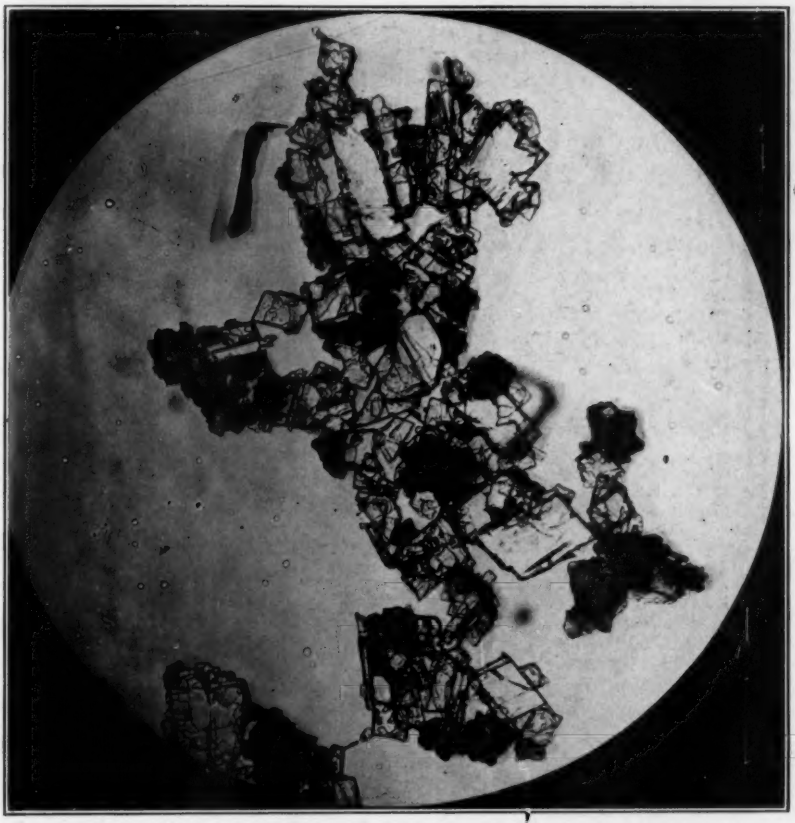

FIG. 11.—Patient P. D. Typical cholesterol crystals and amorphous calcium bilirubinate pigment in the same particle (preoperative specimen of bile).

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The microscopic examination of the bile in our cases proved to be of more diagnostic value than cholecystography (oral method). As can be seen from Table 2, of the 69 patients who were observed there were 63 cases (91.3 per cent) of calculous and non-calculous cholecystitis which were detected by means of bile microscopy, whereas only 56 of these cases (81.2 per cent) were revealed by the cholecystograms. Similar findings were reported by Bockus[11] and his co-workers in their series of gall stone cases.

To summarize, it should be borne in mind that gall bladder disease is at times very difficult to diagnose. This is especially so in patients with a misleading history or negative roentgenographic findings, or both. Therefore, in an attempt definitely to eliminate calculous or non-calculous cholecystitis in doubtful cases, the patients should be given the diagnostic benefit of bile microscopy.

CASE 1.—Where the history, cholecystography and bile microscopy were in agreement.

S. A., male, aged 37 years, gave a history of attacks of biliary colic on and off for 3 years. Physical examination revealed an enlarged gall bladder. The icterus index was 7.2 and the blood cholesterol was 179 mg. per 100 cc. of serum. In the bile, numerous typical and atypical cholesterol crystals were seen (Figs. 1 and 2). Cholecystography revealed many non-calcified cholesterol calculi in the gall bladder. The patient was operated upon and numerous cholesterol stones were found. Upon examining the scrapings of the biliary calculi, typical and atypical cholesterol crystals were observed (Fig. 3).

CASE 2.—Where the history and bile microscopy were in agreement but the roentgenographic examination was negative.

Mrs. R. B., aged 33 years, gave a typical gall bladder history of 18 months' duration. Cholecystography revealed a normal functioning gall bladder. The icterus index was 6.5 and the blood cholesterol was 169 mg. per 100 cc. of serum. A microscopic examination of the bile showed many typical and atypical cholesterol crystals and calcium bilirubinate pigment—amorphous type (Fig. 4). The patient was operated upon and 12 small stones were found in the gall bladder and one in the common duct. When scrapings of the calculi were examined, they revealed similar crystalline elements as were seen in a preoperative specimen of bile (Fig. 5).

CASE 3.—Illustrates the calcium carbonate type of crystal.

Mrs. B. G., aged 65 years, complained of periodic attacks of pain in the right upper quadrant for 6 years. The bile showed many calcium carbonate crystals in addition to typical cholesterol crystals and calcium bilirubinate pigment. The Graham test revealed 3 calculi in the gall bladder. This finding was corroborated at the operation. The icterus index was 7 and the blood cholesterol was 287 mg. per 100 cc. of serum. Upon examining one of the stones, whitish elevated areas were seen on the outer surface. On rubbing one of these areas on a slide, calcium carbonate crystals (Fig. 6) were seen similar to those observed in the preoperative specimen of bile. The inner surface of the stone was composed of cholesterol crystals and calcium bilirubinate pigment.

CASE 4.—Illustrates a case in which bile microscopy was the only method of examination whereby the diagnosis was made.

Mr. N. S., aged 45 years, gave a history of periodic attacks of temperature and exhaustion about once every 6 months. He never had any abdominal pain, but complained of nausea and distention after eating. He rarely vomited. A physical examination was negative. Repeated examinations of the gastric contents revealed a persistent achlorhydria. Roentgen ray of the kidney, teeth, gastro-intestinal tract and gall bladder were negative The icterus index was 5.6 and the blood cholesterol was 321 mg. per 100 cc. of serum. Bile microscopy showed numerous typical cholesterol crystals and amorphous calcium bilirubinate pigment in the same particle (Fig. 7). An exploratory laparotomy was performed. Six small calculi were found in the gall bladder. The bile from the latter showed similar cholesterol crystals and amorphous pigment as were seen in the preoperative specimen of bile (Fig. 8).

CASE 5.—Illustrates the fact that the diagnosis was definitely made by bile microscopy.

Mrs. M. D., aged 37 years, gave a history of having had a burning sensation in the epigastrium, on and off for 3 years. She never experienced any pain. The burning sensation at times would come on 2 hours after meals, and at other times there was no relation to food. A gastro-intestinal series showed a marked pylorospasm, but no definite deformity. At the end of six hours about one-fourth of the barium meal was still in the stomach. Gastric analysis showed free hydrochloric acid of 90; total acidity of 120; blood, positive. Cholecystography did not reveal any definite pathology. The icterus index was 4 and the blood cholesterol was 229 mg. per 100 cc. of serum. The patient had been treated unsuccessfully by various "ulcer cures" and, finally, an examination of the bile was made. It showed calcium bilirubinate pigment—granular and amorphous types (Fig. 9) and few typical cholesterol crystals. At operation no visible or palpable ulcer was found, but the duodenum was very much dilated. The liver was the seat of a marked fibrosis around the gall bladder bed. The gall bladder was very much thickened and adherent, but no stones were found. A cholecystectomy was performed. The bile from the gall bladder showed calcium bilirubinate pigment, granular and amorphous types (Fig. 10), and a few cholesterol crystals. The pathologic report of the gall bladder was "chronic catarrhal cholecystitis."

CASE 6.—Illustrates a case of a penetrating duodenal ulcer associated with calculous cholecystitis in which the gall bladder disease was definitely diagnosed by bile microscopy.

Mr. P. D., aged 34 years, gave a typical ulcer history, with pain 3 hours after meals and relieved by food. A gastro-intestinal series revealed roentgenographic evidence of a penetrating duodenal ulcer. Cholecystography showed a somewhat enlarged gall bladder which functioned very well. The icterus index was 6.2 and the blood cholesterol was 257 mg. per 100 cc. of serum. A preoperative specimen of bile, however, revealed many typical cholesterol crystals and calcium bilirubinate pigment in the same particle (Fig. 11). The patient did well for a time on medical treatment and then had a recurrence of his symptoms. This time the pain was more persistent and was not relieved by food. The patient subsequently came to operation. A duodenal ulcer and an enlarged gall bladder imbedded in a mass of adhesions were found. In the gall bladder there were 2 calculi, each about the size of a pea. A gastro-enterostomy and cholecystectomy

were performed. The scrapings of the stones and the bile from the gall bladder showed calcium bilirubinate pigment and cholesterol crystals as were seen in the preoperative specimen of bile.

Conclusions. 1. Various types of biliary crystals found in preoperative specimens of bile were compared with the crystalline elements found in the scrapings of calculi or bile removed from the gall bladder at the time of operation.

2. In 91.3 per cent of the cases the presence of these crystals in the bile, preoperatively, indicated calculous or non-calculous cholecystitis, irrespective of the history or radiographic findings.

3. Bile microscopy should be employed more frequently, especially in patients with a more or less persistent gastric history.

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REVIEWS.

ALCOHOL AND MAN. Edited by HAVEN EMERSON, M.D., De Lamar Institute of Public Health, Columbia University. Associate editors: HENRY A. CHRISTIAN, M.D., and REID HUNT, M.D., Harvard University; ARTHUR HUNTER, LL.D., F.A.S., New York Life Insurance Company; CHARLES C. LIEB, M.D., Columbia University; WALTER R. MILES, PH.D., Yale University; ERNEST G. STILLMAN, M.D., Rockefeller Institute for Medical Research. Pp. 451; illustrated with tables. New York: The Macmillan Company, 1932. Price, $3.50.

No substance that enters the human stomach has been more exhaustively studied or caused more acrimonious controversy than has alcohol. In the belief that "education in the basic facts about alcohol was essential to the best interests of modern man and his social organization, whether or not legislation was to be a permanent factor in determining the extent to which commerce in beverage alcohol was to be permitted," the authors have endeavored to "assemble and present for the use of the educated laity all the certain facts about alcohol in its biologic and human relationships which are well known and universally taught in the schools of medicine in this country today." They wisely have scrupulously avoided wet or dry advocacy or implications, being sanguine enough to believe that "all persons . . . will in rational periods of the fight pay attention to evidence." They are careful to add that none of the work has been supported in any way by wet or dry advocates. The effects of alcohol on man's conduct and mentality (chapters by Walter Miles, Adolph Meyer and Herman Adler) are treated in the greatest detail, but adequate consideration is also given to the physiologic and pharmacologic effects of alcohol, its effects on the cell and on heredity, on body resistance and longevity, its action as a poison and a medicine and the lesions that it produces. Making due allowance for individualities, one cannot but be impressed and aided by such authoritative statements as "On the brain alcohol in all doses is a depressant;" "most of the alcohol consumed is oxidized and supplies energy for the work of life;" "the habitual use of alcohol in moderate amounts . . . appears to be without any permanent organic effect deleterious in character;" "it is highly improbable that the quality of human stock has been at all injured or adversely modified by the long use of alcohol;" "the utilization of alcohol and alcoholic beverages . . . has decreased greatly and is continuing to decrease;" "total abstainers are . . . longer lived than non-abstainers; moderate users of alcohol . . . are probably as long lived as total abstainers."

E. K.

THE CHILD AND THE TUBERCULOSIS PROBLEM. By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P., Professor of Preventive Medicine, University of Minnesota, Chief of the Medical Staff, Lymanhurst School for Tuberculous Children. With an Introduction by WILLIAM P. SHEPARD, M.D., F.A.P.H.A., Welfare Director, Western Division, Metropolitan Life Insurance Company. Pp. 230; 19 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $3.00.

THIS book will be of great value to physicians who have not had much experience in the field of childhood tuberculosis, to nurses, to all intelligent

public health officers, to social workers and particularly to school executives and other administrators who have to do with the health problems of childhood and youth. The author starts with the thesis that tuberculosis is a highly communicable disease to be controlled by the same methods as are effective in other contagious diseases, the first of which is prevention by stoppage at the source. He has departed from the old and still current view that tuberculosis in childhood, after recovery, immunizes sufficiently against further infection and is, therefore, to be looked upon as a protective mechanism inevitably attendant upon modern civilization. He cites many case records to prove his point, and clearly shows, out of the records of large experience in institutions with which he is connected, the manner in which childhood disease, so far from protecting against later tuberculous complications, actually prepares the way for the familiar adult disease. At the same time he points out the steadily lessening incidence of positive tuberculin reactions in children of many American communities, and urges the routine of frequent use of the tuberculin test in schools and in medical practice by family physicians as the most practical way to locate tuberculous infection early in its course when remedial measures can prevent it from passing into clinical disease. His argument on the small cost of early diagnosis as compared with the high cost of prolonged institutional treatment is thoroughly sound. The last chapter is a very able summary of the measures to be employed in an antituberculosis campaign of prevention. The book is of small but convenient size, excellently handled by the publisher.

E. L.

DISEASES OF THE SPINAL CORD. By WILLIAMS B. CADWALADER, M.D., Professor of Clinical Neurology, University of Pennsylvania Medical School, etc. Introduction by WILLIAM G. SPILLER, M.D., Professor of Neurology, University of Pennsylvania Medical School. Pp. 204; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, $5.00.

THIS book is warmly commended by Professor Spiller, whose deep concern, in turn, is gratefully appreciated by the author. One would expect and finds much pathologic detail. At times it appears that the usefulness of the volume would be enhanced by more serious consideration of treatment. We are told: "The general practitioner will here find suggestions as to treatment," only to find it frequently discussed in a single sentence. A noteworthy exception is the treatment of acute anterior poliomyelitis.

Though highly scientific, the subject-matter is at all times concisely and lucidly presented and aptly illustrated throughout. There is an embodied wealth of opinion by others which is always carefully documented.

N. Y.

AN INTRODUCTION TO ZOÖLOGY. By ZENO PAYNE METCALF, D.Sc., Professor of Zoölogy, North Carolina State College. Pp. 425; 184 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $3.50.

THIS is a book of distinctive character, stressing function and using for detailed study as a type of the vertebrates, the rat. The author believed the use of a mammal preferable for students both as a better known type and as more significant for human biologic problems. The work is divided

into three parts, the first being introductory, the second dealing with the morphology and physiology of the rat and the third considering the philosophic implications of the facts disclosed. A constant effort is made to correlate structure and function. Each chapter is preceded by an analytical outline. The illustrations are numerous, of an excellent quality and mainly original. They are used to present structural details and to give an insight into general conditions difficult to describe briefly. There are a number of excellent and well-constructed diagrams of practical value, and a good index. Typographically the book is very pleasing. It should prove of great help to teachers who employ the author's method of presenting an introductory course in zoölogy. C. McC.

DIAGNOSIS AND TREATMENT OF DISEASES OF THE THYROID GLAND. By GEORGE CRILE and Associates. Pp. 508; 164 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $6.50.

THIS is not to be regarded as a formal treatise on the thyroid gland; "it is rather an account of the experience of the Staff of the Cleveland Clinic in the treatment of diseases of that organ."

The sections on iodin and the thyroid gland are exceedingly well written and covers a wealth of material in a relatively short space. In the chapter on The Rôle of the Thyroid Gland in the Energy System, the author postulates in a field which is as yet debatable. The chapter on Endemic Goiter is short but adequate. Carbohydrate metabolism in hyperthyroidism is well discussed by Dr. John. The sections on the clinical symptoms are written from a large clinical experience. While an entire chapter is devoted to the various blood pictures, hardly a page is given to basal metabolism. This is unfortunate.

The photographs and roentgenograms are excellent and better than some of the drawings illustrating operative procedures.

The book is valuable as giving the experiences of a large thyroid clinic. It could have been more carefully edited and would in numerous instances have been more convincing if certain material could have been presented as hypothetical rather than as experimental fact. I. R.

MEDICINE AMONG THE AMERICAN INDIANS. Vol. VII of Clio Medica. By ERIC STONE, M.D. Pp. 139; 17 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, $1.50.

ALTHOUGH they lived in a Stone Age culture, the American Indians in their medical practices were far in advance of the Stone Age, equaling, for example, the medical knowledge and practices of the Assyrians or the early Greeks. Moreover, their treatment of wounds, fractures and empyema was equal to or better than that of the white physicians of the 18th century, and in the management of retained placenta they anticipated Credé by a century. They added 59 drugs to our modern pharmacopoeia, including cascara and lobelia. Heretofore the material on the medical practices of the Indians has been hidden in short fragments under a mountain of other lore. In gathering this material for the first time under one cover—a task that has been very creditably carried out in this convenient pocket-sized volume—the author has performed a real service.

R. K.

MINOR SURGERY OF THE URINARY TRACT. By HERMON C. BUMPUS, JR., PH.B., M.D., M.S., F.A.C.S., Associate Professor of Urology, The Mayo Foundation. With a chapter on Caruncles by JOHN L. CRENSHAW, M.D., Associate Professor of Urology, The Mayo Foundation, and a chapter on Postoperative Care by ANSON L. CLARK, M.E., M.D., Section on Urology, The Mayo Clinic. Pp. 124; 57 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $3.00.

THIS splendid little book details in great clearness the technical treatment of urologic conditions by instrumental methods. No attempts are made to outline symptoms or diagnostic steps, for it is intended for the guidance of one already proficient in these departments. The subjects covered are caruncle of the urethra, stricture of the urethra, hypertrophy of the prostate, carcinoma of the prostate, stone in the bladder, tumor of the bladder, bladder infection and ulcer, and stone in the ureter. One wonders, on the one hand, when such serious pathologic states are being treated, whether the term "minor surgery" is justified; while, on the other hand, it is a delightful commentary on the startling advances accomplished in this field in the last two decades through instrumental methods, for it is to this phase of therapy that this book is almost exclusively limited.

A. R.

LES RÉTICULOCYTES ET LES RÉTICULOCYTOSES. By DR. C.-M. LAUR, Préparateur Adjoint a la Faculté de Médecine de Paris. Preface by PROF. N. FIESSINGER. Pp. 160; 3 figures and 4 plates in colors. Paris: G. Doin & Cie, 1932. Price, 35 fr.

ALTHOUGH these immature erythrocytes have been recognized and studied in the circulation since the time of Ehrlich, it was not until the past decade that their great practical value in clinical medicine was realized in connection with Minot's work on the liver treatment of pernicious anemia. No extended systematic study, however, of their various manifestations and significance has been attempted until Fiessinger, the eminent French hematologist, stimulated the present work. This richly documented statement is divided into 6 chapters covering the history of the subject, technique, nature of reticulocytes and their behavior under normal and pathological condition. It should prove very useful to hematologists.

E. K.

THE COLON, RECTUM AND ANUS. By FRED W. RANKIN, B.A., M.A., M.D., F.A.C.S., Division of Surgery, The Mayo Clinic; Associate Professor of Surgery, The Mayo Foundation; J. ARNOLD BARGEN, B.S., M.D., M.S. in Medicine, F.A.C.P., Division of Medicine, The Mayo Clinic; Assistant Professor of Medicine, The Mayo Foundation; and LOUIS A. BUIE, B.A., M.D., F.A.C.S., Section on Proctology, The Mayo Clinic; Associate Professor of Proctology, The Mayo Foundation. Pp. 846; 435 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $9.50.

THIS monograph should take first rank in the literature on the lower bowel and anus. Extensive clinical and laboratory facilities have combined to give the authors an experience and grasp of the subject rarely equalled. The complete chapters on anatomy and physiology include a full discussion of the nerve supply of the bowel, a subject of increasing importance in these days of sympathetic nerve surgery. The various diseases of the colon, such as megacolon, volvulus, intussusception, diverticulitis, the

granulomata, etc., are treated in detail, while the chapter on chronic ulcerative colitis is largely a summary of Bargen's extensive work in this disease. Because tumors of the large gut represent such a large portion of colon diseases their diagnosis and treatment have been fully discussed. Buie has added a well-written section on minor surgical diseases of the anus. A short, well-illustrated chapter by Lundy discusses anesthesia in operations on the large gut. In the final technical section are described and illustrated the various operative procedures which the authors use in the treatment of their cases.

The book should make a particular appeal to the general surgeon and to the gastro-enterologist, as the latest and most up-to-date work on its subject.

L. F.

SCIENTIFIC AND ESOTERIC STUDIES IN SEXUAL DEGENERATION IN MANKIND AND IN ANIMALS. By PROFESSOR CHARLES SAMSON FÉRÉ. Translated by ULRICH VAN DER HORST, PH.D. Pp. 325. New York: The Falstaff Press, 1932. Price, $6.00.

ACCOUNTS and discussions of sexual perversions are undoubtedly nasty reading for some people, and without emotional connotations for the objective scientist. But it must also be recognized that unfortunately they are pleasantly erotic for the pornographically minded. Their importance, however, in the pathologic physiology of sex cannot be overlooked on this account, and an ostrich policy toward the subject on the part of the medical profession will necessarily have the usual disastrous results. It seems obvious, then, that their distribution should be limited as far as possible to the appropriate scientific readers. This is apparently attempted for the present translation by restrictions placed on its sale, though it must be recognized that the type of its advertisement, cover and frontispiece, and the inclusion of "esoteric" in the sub-title do not tend to support this view. Except for this qualification, and perhaps a laxity of standard of observational control, we find no fault with the subject matter, though we may not agree with many of the opinions expressed. The number of observations on a great variety of animals are sufficiently correlated with human abnormalities of behavior to afford a valuable lateral attack on the evaluation of the latter. Just as comparative pathology is an important department in the study of somatic disease, so should proper investigations in comparative psychology lead to noteworthy advances in the field of psychiatry.

E. K.

CLASSIC DESCRIPTIONS OF DISEASE. By RALPH H. MAJOR, Professor of Medicine, University of Kansas School of Medicine. Pp. 630; 127 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $4.50.

THE potency of such works as this in enlivening acquaintance with the history of medicine has already been stressed in these columns in connection with Camac's Epochmaking Contributions, Long's Readings in Pathology and Fulton's Selected Readings. The more such anthologies are added to, if well selected and accurately edited, the more widely may knowledge of the master medical writings be spread among the medical profession and integrated, in the Oslerian manner, with the practical education of the medical student. Pursued through all the major branches of medicine, this method also will bring these gems to hundreds of centers that never could have attained possession of a like number of originals. The author is to be congratulated on the soundness of his selection, in fact the very

excellence of the production leads to the criticism that it is unfortunate that more "classical descriptions" are not included. The book could well have been half as long again (without encroaching on other fields) and twice as valuable. Even though bacteriologic and neurologic (and apparently parasitic) diseases have intentionally been omitted, such conditions as (to name but a few of some 50 or more that come to mind) infantilism, poliomyelitis, lethargic encephalitis, the two hemolytic jaundices, mononucleosis, arteriosclerosis, noma, argyria, blackwater fever and dengue, rubella and whooping cough might well have been included. Descriptions of "carriers" in disease are conspicuous by their absence, also such names as Ayerza, Banti, Gaucher, Niemann, v. Recklinghausen and others too numerous to mention, even though the pertinent passages to be included would need to be often but a few lines in length.

Granted that there is hardly an end to such possible additions, that cost must be considered and that no selection by one would entirely suit another, the Reviewer would have preferred to have seen many such as these included, even at the expense of, for example, some of the 6 articles on myxedema, the 7 on lead poisoning, 9 on aortic insufficiency, 10 on gall stones, etc., or, better still, in addition to them. Perhaps more can be included in the second edition that will sooner or later be required or perhaps a second volume published. Even without such additions, however, we repeat our congratulations to the author on his extremely valuable production.

E. K.

THE NATURE OF HUMAN CONFLICTS. By A. R. LURIA, Professor of Psychology at the Academy of Communistic Education; Research Associate, State Institute of Experimental Psychology, Moscow. Translated from the Russian and edited by W. HORSLEY GANTT, Phipps Psychiatric Clinic, Johns Hopkins University, etc. With a Foreword by ADOLF MEYER, Professor of Psychiatry, Johns Hopkins University. Pp. 428; 133 illustrations. New York: Liveright, Inc., 1932. Price, $4.00.

THIS book, by one of the foremost Russian psychologists, is concerned largely with laboratory experiments done on human beings. The experiments consist of kymographic recording of motor responses of both right and left hand and speech responses from a wide range of subjects, as well as descriptive studies of gross behavior of the subject. The purposes of the research are: (1) to find out the origin of the mechanisms lying at the basis of the disorganization of human behavior, and (2) to see if some approach to proper conceptions of regulation of behavior might be evolved.

The conception of the "functional barrier" is presented as something existing in the activity of the nervous system which stands between the original excitation and the higher centers and, more or less according to the needs of the organism, interferes with its outlet in the motor sphere. This functional barrier is considered to be "of cultural origin"—a functional inclusion in the organism. The studies carried out with the children show that the functional barrier does not exist in early years of childhood but is elaborated later. Experiments are described in which affect and conflict have served to destroy this functional barrier which brings about "disorganization of behavior." Studies of neurotics are included in which this same destruction has taken place, and it is suggested that this may serve to explain the occurrence of the neurosis.

One envies the opportunities this laboratory has had for experimental material: almost 20 persons accused or involved in murder were given over to the laboratory for these experiments before they were directly accused of their crime or questioned by police!

The results of the experiments are used to explain the origins of difficulty in various mental, neurologic and nervous conditions. These conclusions are perhaps too far fetched but nevertheless give us a nice correlation between the functional and organic fields, as viewed by the laboratory psychologist on a basis of actual experimental material.

As a whole, the book is an important and extremely interesting production, opening new opportunities for associated studies in medicine and psychiatry. It introduces some new viewpoints and methods that are original, not exactly in character, but rather as regards the interpretations and conceptions secured. The material might have been condensed, for the discussions come to point slowly. The book can be read with profit by all psychologists and every scientific medical thinker. L. S.

BOOKS RECEIVED.

NEW BOOKS.

Publications of the Committee on the Costs of Medical Care. No. 25. *The Ability to Pay for Medical Care.* By LOUIS S. REED, PH.D. Pp. 107; various tables. Price, $2.00. No. 26. *The Incidence of Illness and the Receipt and Costs of Medical Care Among Representative Families.* Experiences in Twelve Consecutive Months during 1928–1931. By I. S. FALK, PH.D., MARGARET C. KLEM, and NATHAN SINAI, D.P.H. Pp. 327; various figures and tables. Price, $3.00. No. 27. *The Costs of Medical Care.* A Summary of Investigations on the Economic Aspects of the Prevention and Care of Illness. By I. S. FALK, PH.D., C. RUFUS REMEM, PH.D., C.P.A., and MARTHA D. RING. With a Foreword by RAY LYMAN WILBUR, M.D., Chairman of the Committee. Pp. 623; 47 figures and various tables. Price, $4.00. Chicago: The University of Chicago Press, 1933.

No. 27 is a summary of the five years of intensive, scientific investigation of the Committee on the Costs of Medical Care—being a résumé of the 26 volumes of publications on specific aspects of the prevention and care of illness which have preceded this volume. For the review of the Final Report of the Committee on the Costs of Medical Care (*Medical Care for the American People*, Publication No. 28), see AM. J. MED. SCI., 1933, **185**, 574.

Annals of the Pickett-Thomson Research Laboratory, Vol. VIII. *The Common Cold.* By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), and ROBERT THOMSON, M.B., CH.B. (EDIN.). Pp. 738; illustrated, and 51 pages plates. Baltimore: The Williams & Wilkins Company, 1932. Price, $15.00.

International Clinics, Vol. 1, Forty-third Series, March, 1933. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, with the Collaboration of Twelve Associates. Pp. 305; 16 illustrations, 1 colored plate. Philadelphia: J. B. Lippincott Company, 1933. Price, Cloth, $3.00.

Human Values in Psychological Medicine. By C. P. BLACKER, M.C., M.A., M.D., M.R.C.P. Pp. 179. New York: Oxford University Press, 1933. Price, $2.50.

The Committee on the Costs of Medical Care. No. 13. *The Ross-Loos Medical Group.* A Description of a Voluntary Health Insurance Plan. By ALDAN B. MILLS and CAMERON ST. C. GUILD, M.D., DR. P.H. Pp. 59. Abstract of Publication No. 26. *The Incidence of Illness and the Receipt and Costs of Medical Care Among Representative Families.* By I. S. FALK, PH.D., MARGARET C. KLEM, and NATHAN SINAI, D.P.H. Pp. 18. Washington, D. C.: The Committee on the Costs of Medical Care, 1933.

Syphilis des Herzens und der Gefässe. Vol. 16 of Medizinische Praxis, Sammlung für Arztliche Fortbildung Herausgegeben von L. R. GROTE, A. FROMME, K. WARNEKROS. By Prof. Dr. ED. STADLER, Leitender Arzt der Inneren Abteilung des Stadtkrankenhauses Plauen i. V. Pp. 82; 8 illustrations. Leipzig: Theodor Steinkopff, 1932. Price, Paper, Rm. 6.50; Cloth, Rm. 7.80.

Roundabout Harley Street. The Story of some Famous Streets. By CYRIL PHILLIPS BRYAN, M.D., B.CH., etc. Pp. 260. London: John Bale, Sons & Danielsson, Ltd., 1932. Price, 5s.

The Rise of Preventive Medicine. University of London Heath Clark Lectures, 1931 delivered at The London School of Hygiene and Tropical Medicine. By SIR GEORGE NEWMAN, K.C.B., M.D., F.R.C.P., HON. D.C.L., LL.D., Chief Medical Officer of the Ministry of Health. Pp. 270; illustrated. New York: Oxford University Press, 1932. Price, $3.00.

The Medical Clinics of North Amierica, Vol. 16, No. 5 (Baltimore Number, March, 1933). Pp. 257; 16 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, Paper, $12; Cloth, $16.

FORTY YEARS OF PSYCHIATRY. *Nervous and Mental Disease Monograph Series No. 57.* By WILLIAM A. WHITE, A.M., M.D., SC.D. Pp. 154. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1933. Price, $3.00.

American and Canadian Hospitals. A Reference Book giving Historical, Statistical and other Information on the Hospitals and Allied Institutions of the United States and Possessions, and the Dominion of Canada. Edited by JAMES CLARK FIFIELD, with the coöperation of the American Hospital Association. Pp. 1560; 1 colored illustration. Minneapolis: Midwest Publishers Company, 1933. Price, $10.00.

Scientific and Esoteric Studies in Sexual Degeneration in Mankind and in Animals. By PROFESSOR CHARLES SAMSON FÉRÉ. Translated by ULRICH VAN DER HORST, PH.D. Pp. 325. New York: The Falstaff Press, 1932. Price, $6.00. (For review see p. 864.)

NEW EDITIONS.

The Science and Practice of Surgery. In 2 volumes. *Vol. I. General Surgery; Vol. II, Regional Surgery.* By W. H. C. ROMANIS, M.A., M.B., M.CH. (CANTAB.), F.R.C.S. (ENG.), F.R.S. (EDIN.), Surgeon and Lecturer on Surgery, St. Thomas's Hospital, etc., and MITCHINER, PHILIP H., M.D., M.S. (LOND.), F.R.C.S. (ENG.), Hon. Surgeon to H. M. The King, etc. Pp. 1762 and 148 pages of Index; 752 illustrations. Fourth edition. Philadelphia: Lea & Febiger, 1933. Price, $12.00 set.

Diseases of the Skin. By the late ROBERT W. MACKENNA, M.A., M.D., B.CH. (EDIN.), Sometime Lecturer in Dermatology at the University of Liverpool; Honorary Dermatologist, Royal Infirmary, Liverpool, etc. Third Edition Revised and Enlarged by ROBERT M. B. MACKENNA, M.A., M.D., B.CH. (CAMB.), M.R.C.P. (LOND.), M.R.C.S. (ENG.), Honorary Consulting Dermatologist, Liverpool Heart Hospital, etc. Pp. 506; 149 text illustrations, 45 colored plates. Baltimore: William Wood & Co., 1933. Price, $8.00 (Temp. price, $6.00).

Like the earlier editions, this book makes a good compromise between brevity and adequacy. The classification is as far as possible etiologic. The illustrations are excellent, the colored plates being especially realistic.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Inequality of Blood Pressure in the Brachial Arteries, With Especial Reference to Disease of the Arch of the Aorta.—KORNS and GUINAND (*J. Clin. Invest.*, 1933, **12**, 143) state at the beginning of their contribution that it has been assumed that in normal persons the blood pressure and the volume of the pulse are equal in the right and left brachial and carotid arteries, and as a correlary, that sphygmic inequality in these arteries is evidence of disease of the aorta except under certain anomalous and unusual circumstances. As a rule, in the great majority of instances some pathologic process such as syphilitic aortitis has resulted in narrowing of the main branch of the aorta at its origin. Several instances are given in which inequality of blood pressure in the arms was observed. As there could not be any adequate explanation for this finding, 1000 healthy persons, most of whom were university students, were studied. The average age of this group was 20 years and no evidence of cardiovascular disease could be found. The blood pressure was taken simultaneously, with mercury manometers, in the two arms. The maximum systolic pressure was found to be greater in the right than in the left arm in 19.3 per cent of cases and in the left arm greater than the right in 2.9 per cent. The minimum diastolic pressure was greater in the right arm than in the left arm in 12.7 per cent, whereas the left was greater than the right in 9 per cent. These inequalities in most instances were greater than 11 mm. of mercury. There were thus found to be 439 instances of inequalities in 378 persons and nearly three-fourths of the high pressures were dextro-lateral. Significant inequalities in the pulse pressure occurred in 274 people, the average inequality being 14.3 with a maximum of 38 in the right arm as contrasted with the left, whereas the inequality in the left arm was greater than in the right in about one-third as many instances, although the average and maximum inequalities were about equal. These sphygmic inequalities probably occur in all normal individuals at some time or another but without organic disease are probably always transitory. They may involve only the systolic or the diastolic pressure or both, but in the great majority of instances it is greater in the right than in the left arm. The right- or left-handedness of the individual seems to play no part in this circulatory phenomenon. The physiology is not understood, but it should be definitely comprehended that sphygmic inequalities in the brachial arteries are a sign of disease of the aorta or its branches only when they are permanent.

SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.,
J. WILLIAM WHITE PROFESSOR OF SURGICAL RESEARCH, UNIVERSITY OF PENNSYLVANIA,
AND
C. G. JOHNSTON, M.S., M.D.,
INSTRUCTOR IN SURGERY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

Cholesterol and the Gall Bladder.—There has been a long controversy as to whether cholesterol is absorbed from, excreted into, or merely concentrated in the bile of the normal gall bladder. NAUNYN (*A Treatise on Cholelithiasis*, London, New Sydenham Society, 1896) supported the hypothesis that the gall bladder and extra-hepatic bile ducts secreted cholesterol into the bile. In this contention he was supported by his many students and associates. On the other hand, ASCHOFF (*Münch. med. Wchnschr.*, 1906, **53**, 1847) and his school have maintained that cholesterol is absorbed from the bile through the gall bladder wall. Data on this controversial point are important because of the relationship which cholesterol bears to calculus formation.

Among those who have within recent years supported the Naunyn hypothesis are TORINOUMI (*Beitr. path. Anat. u. allg. Path.*, 1924, **72**, 456), ILLINGWORTH (*Brit. J. Surg.*, 1929, **17**, 203), BOYD (*Ibid.*, 1923, **10**, 337) and ANDREWS, SCHOENHEIMER and HRDINA (*Proc. Soc. Exp. Biol. and Med.*, 1931, **28**, 945). Of the above papers Illingworth's conclusions were undoubtedly based upon insufficient data. Boyd did not actually measure the cholesterol content quantitatively and Andrews, Schoenheimer and Hrdina published no data for critical review. Torinoumi, however, found that cholesterol was absorbed from the normal gall bladder but excreted into the infected viscus.

ELMAN and TAUSSIG (*Proc. Soc. Exp. Biol. and Med.*, 1931, **28**, 1006; *J. Exp. Med.*, 1931, **54**, 775) and ELMAN and GRAHAM (*Arch. Surg.*, 1932, **24**, 14) have reinvestigated this very important subject. These authors concluded that both the concentration and the total amount of cholesterol increased in the hepatic bile when it was subjected to the activity of the gall bladder. Their work is open to the criticism that in the dog their studies cannot be considered quantitative. However, their studies on the human are important in that in the presence of gall bladder disease they demonstrated that the gall bladder did secrete cholesterol.

RIEGEL, JOHNSTON and RAVDIN (*J. Exp. Med.*, 1932, **56**, 1), after a study of the fate of cholesterol in hepatic bile when subjected to the activity of the normal gall bladder, concluded that cholesterol is not secreted into or absorbed from such a viscus. Their observations, which were made by a method which has been proven to be satisfactory for quantitative studies, led them to conclude "as did ROUS and MCMASTER (*J. Exp. Med.*, 1921, **34**, 47) with regard to bile pigment, that normally there is no absorption of cholesterol . . . save in the case of the infected gall bladder." In the infected gall bladder evidence was

obtained to support the observations of Elman and Graham. Since the papers of Elman and his associates and those of Riegel and her associates were published, two other papers have appeared which merit review. WILKIE and DOUBILLET (*Arch. Surg.*, 1933, **26**, 110) propose an ingenious action of the gall bladder wall. If the bile cholesterol is high, absorption will occur from the bile to the blood; while if the blood cholesterol is high, the cholesterol will pass from the blood to the gall bladder bile. It should be pointed out that in quantitative experiments reported by Riegel, Johnston and Ravdin where the hepatic bile of the dog (with concentrations varying from 11 to 46 mg. per 100 cc. of bile) were subjected to the activity of the normal gall bladder, there was no evidence that such a mechanism existed and that when one considered the concentration of the hepatic bile after its entrance into the gall bladder no excess of cholesterol could be demonstrated even though it is well known that the blood cholesterol of the dog is high.

A more recent paper by ANDREWS, DOSTAL and HRDINA (*Arch. Surg.*, 1933, **26**, 382) adds further evidence to the earlier observations of Riegel, Johnston and Ravdin as regards the normal gall bladder and to the evidence reported by Elman and Graham as regards the infected gall bladder.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

The Influence of Thyroxin on Avertin Narcosis.—It has been claimed that even relatively large doses of avertin fail to induce deep sleep in cases with hyperthyroidism. The intravenous administration of thyroxin as an antidote in severe avertin narcosis has also been suggested. The most reliable objective measure of the duration and depth of avertin narcosis is its concentration in the blood. NELL (*Klin. Wchnschr.*, 1932, **11**, 367), therefore, undertook the measurement of the concentration of avertin in the blood and the duration of sleep in a group of control subjects, and in a second group which received 0.2 mg. of thyroxin ½ hour or 1 hour after the administration of avertin. A third group of patients received the thyroxin 1 hour before the administration of avertin. In a fourth group thyroxin was administered in amounts that produced elevation of the basal metabolism alone, or in addition symptoms of thyrotoxicosis. From 0.1 to 0.125 gm. of avertin per kilogram of body weight was administered. On the basis of such a carefully controlled study the author claims that thyroxin in amounts described does not influence either the concentration of avertin in the blood or the duration of sleep. If thyroxin previous to

the time of anesthesia produces an elevation of the basal metabolism without symptoms, the duration of narcosis is shortened, not because of the increased rate of destruction of avertin in the body, but because of the low absolute concentration in the blood. Patients with symptoms of thyrotoxicosis, on the other hand, showed a deep and prolonged sleep with a corresponding high avertin concentration in the blood.

PEDIATRICS

UNDER THE CHARGE OF
ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Diphtheria Control in Chicago.—BUNDESEN, FISHBEIN and NIBLACK (*J. Am. Med. Assn.*, 1933, **100**, 1093) state that the diphtheria mortality in Chicago has been reduced by having nurses call on the parents of every child up to 8 years of age, urging that the child be taken to the family physician for diphtheria immunization and obtaining signed cards asking that the children be immunized. The maintenance of an active list of all the younger children in a community is most important in carrying out this as well as many other health programs. The authors have found it of extreme value in their diphtheria-prevention campaign. As soon as the child reaches the age of 6 months, a personal call is made on the mother. Continuing this routine it is likely that the diphtheria immunization will be brought to an even higher level and that the mortality and the morbidity rates be reduced to lower levels than have already been attained. It was found that with the alum toxoid a far lesser number of reactions occurred in the children; that there was a more rapid production of the immunity, and a greater percentage of the children became immune with two inoculations. In the light of present knowledge this seems to be the most efficient immunizing agent against diphtheria. In all communities in which there are a large number of foreign-born individuals the coöperation of the church influence proves invaluable in promoting all forms of public health work. Some of the individuals of these races, many of whom have suffered persecution of various types in the countries of their origin, show a tendency to resent what they consider interference with their personal liberty. This can be overcome by the influence of secular advice and it was found to be the greatest single factor producing the success of the reported campaign. The distribution of literature urging diphtheria immunization alone cannot be successful in stimulating the protection of a large proportion of the child population. Such literature has its greatest value in paving the way for the visits of the nurses, whose function should be that of salesmen selling diphtheria immunization. Needless to say the coöperation of the medical societies as well as of the individual physicians is necessary for the successful public health campaign.

An Unusual Encephalopathy Probably Infectious in Origin.—MCINTYRE (*J. Am. Med. Assn.*, 1933, **100**, 1097) reports a series of

20 cases of an unusual type of encephalitis. Hemorrhage into the spinal fluid was a prominent feature, occurring in 13 of the 20 cases. The spinal fluid pressure was definitely increased in only 3 cases. Lymphocytosis was observed in 7 cases. Increase in globulin was noted in 5 cases in which no bleeding occurred into the spinal fluid. This suggests a serous infiltration in those cases with perhaps increased permeability of the pial vessels, which in the more severe forms allowed both red and white blood cells as well as serum to escape from the blood-vessels. Somnolence, at times becoming coma, was a prominent feature as it occurred in 12 of the 20 cases. Coma was present in 9 cases. Diplopia occurred in 6 cases. Pyramidal signs were a prominent sign, occurring in 14 cases. This was in marked contrast to the epidemic of so-called lethargic encephalitis observed by the author, in which extra-pyramidal signs were more prominent than pyramidal signs. Another marked difference in the cases noted in this series from those of epidemic encephalitis was that in this series no extra-pyramidal residues were noted. Convulsions beginning with Jacksonian symptoms passing into generalized convulsions were observed in 7 cases. This indicated motor cortex irritation. Death occurred in 9 cases. Congestion of the disks occurred in 7 cases and a choked disk was observed in 2 cases. Clinically there were 3 types of cases. One group was represented by serous infiltration with clinical meningo-encephalitic signs plus increase in globulin in the spinal fluid. Another group showed clinical meningo-encephalitic symptoms with lymphocytosis in the spinal fluid. The third group was the most severe form of the disease, represented by those cases in which hemorrhage occurred in the spinal fluid, accompanied by increase in globulin and also by increased lymphocytes in the spinal fluid. It is thought that the disease is infectious in origin although no definite evidence was evoked. In differentiation a number of conditions must be considered. These include cerebral arteriosclerosis with hemorrhage; meningeal hemorrhage due to rupture of a syphilitic aneurysm; idiopathic hemorrhage as a result of status lymphaticus; brain tumor with hemorrhage from the tumor; fracture of the skull with meningeal hemorrhage, although this can usually be eliminated by the history. Although this report includes a number of adults, it was seen in a number of children, 1 being only 8 months of age.

Prevention of Scarlet Fever.—MELNICK (*Arch. Pediat.*, 1933, **50**, 158) performed the Dick test on 551 children in an orphanage. Ninety-four of these children (17 per cent) were Dick positive, and 91 of these were immunized with Dick scarlet fever toxin, receiving 5 injections at weekly intervals. The following precautionary measures were found to be valuable in reducing the severity and duration of the reactions. Mild laxative, preferably milk of magnesia, was given on the night before the injections. The diet was restricted on the day before the injections to fruit juices, cereal water, tea and toast. The activities were restricted on the day before as well as the day after the injection. The injection should be given the latter part of the day, late afternoon or early evening, and preferably on Friday or on a day preceding a school holiday, so that if a reaction should appear, confining the child to bed, there will be no necessity for absence from school. The reac-

tions observed in this study were at no time alarming, nor were they productive of any complications or sequelæ such as are frequently observed even in the mild types of scarlet fever. The reactions that were encountered included headaches, nausea, vomiting, abdominal pain and fever in various combinations or separately. Ninety children were Dick tested 2 weeks after the 5th injection, and of this number 79 children (88 per cent) were Dick negative and 11 (12 per cent) were Dick positive. The 11 Dick positives who had already received 5 injections of scarlet fever toxin were given a 6th injection and were tested after 2 weeks with the result that an additional 9 children were rendered Dick negative. A total of 98 per cent of negatives were thus obtained.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Rudimentary Accessory Vagina.—An interesting development defect which has come to the attention of HALBAN (*Zentrlbl. f. Gyn.*, 1932, **56**, 2401) on several occasions is the existence of a band in the vagina which resembles scar tissue but which he has seen in nulliparous women who have never had operative procedures performed on them. He terms this band *plica falciformis cervico-laquearis* and states that as a rule it begins around the upper region of the portio vaginalis of the cervix and extends in an angular fashion along the lateral vaginal fornix and then toward the vulva. Its edge is usually sharp and undermined and presents a characteristic crescentic shape. He believes this band represents the remains of a vaginal septum which has been displaced laterally in the course of development of the vagina. In the space between this band and the true lateral wall of the vagina is a rudimentary second vagina. If there is no communication between these two vaginas the patient may develop a lateral hematocolpos or pyocolpos. If there is a communication between the two vaginas it is possible to demonstrate the second cervix above the rudimentary vagina through the communicating opening. Such a second vaginal sac and cervix will be large or small depending on how high the atresia of the rudimentary vagina extends. When this second vagina communicates with the main vagina there will be no secretion present in the accessory vagina and the walls collapse leaving the above mentioned plica which is gradually displaced laterally. The practical importance of this observation is only that it makes the observer think of a double uterus or other defects of development in such a patient since these defects are frequently unrecognized. This contribution of the author, which has not been previously reported, adds another point of interest to the fascinating subject of defects in fusion of the Muellerian ducts.

Relief of Pain in Pelvic Carcinoma.—In the late stages of carcinoma of the female pelvic organs the pain is sometimes so intense and constant that even morphin is without avail unless given in enormous doses. In such cases GRANT (*Am. J. Obst. and Gynec.*, 1932, **24**, 620) reminds us that the pain can be permanently relieved by the operation of cordotomy which sections the fibers in the anterolateral columns of the spinal cord. Following the operation there is no pain or temperature sensation below the point of section but the sensation of touch and position are unimpaired. While bilateral cordotomy takes longer to perform than the unilateral operation it is to be preferred in the treatment of pelvic cancer because it is more certain in its results. His experience is based on 25 cases of this type in 15 of which a bilateral operation was done and in 10 a unilateral. The average duration of life following the operation was 7 months. The disadvantage of the operation is that unless the incision into the cord is accurately placed, the pain may not be completely relieved or the motor pathways may be damaged, resulting in paralysis of the legs and interference with sphincter control. While this may seem to be a rather heroic type of operation to undertake in inoperable patients, the complete relief of pain during the last months of a lingering illness will at times justify its performance.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Pathologic Changes in the Orbit in Progressive Exophthalmos.—NAFFZIGER (*Arch. Ophthal.*, 1933, **9**, 1) reviews the theories on the causes of exophthalmos, ocular muscle paralysis, and optic nerve involvement in cases of exophthalmic goiter, and mentions the various treatments previously used for the relief of progressive exophthalmos. His own observations were made on 6 cases of progressive or malignant exophthalmos coming on after thyroidectomy for exophthalmic goiter. The exophthalmos varied from 26 to 35 mm. In 5 cases, ocular movements were greatly impaired, especially upward rotation. Swelling of the optic disks was present in 5 cases and impairment of vision in 5, in 1 of these without ophthalmoscopic changes. After other methods failed to control the progression of the exophthalmos, the orbits were decompressed by means of an intracranial removal of the orbital plate and the roof of the optic foramen, and opening of the orbital fascia and the ring of Zinn. The operation was successful in each instance. The globes receded gradually, the recession varying from 2 to 7 mm. without tendency to recurrence. The edema of the disks subsided rapidly and vision improved promptly. In every orbit, the extraocular muscles were found to be greatly enlarged. The muscles meas-

ured from 3 to 8 times their normal size, and showed histologically varying degrees of interstitial edema, degeneration, fibrosis and cellular infiltration. In the later phases, scar tissue and hyaline change were found in the muscles. In some sections the walls of the arterioles were thickened and infiltrated by mononuclear cells. The author believes that this swelling and degeneration of the muscles accounts for the exophthalmos and for the impaired ocular rotations. He adds that enlargement of the extraocular muscles in cases of exophthalmos had been observed by previous investigators, but that its significance had not been properly appreciated.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Time Factors Concerned in the Germicidal Action of Ultraviolet Light.—Ultraviolet light has become a fixture in the therapeutic armamentarium of the otolaryngologist. Like many other physiotherapeutic procedures, ultraviolet light's action has been rather poorly understood and, in consequence, its clinical application has been injudiciously exploited. Therefore it behooves us to recognize basic contributions which shed a ray of light on the problem at hand. The effect of radiant energy has long been known to be the result of a certain intensity working in a given period of time, during which period a definite amount of energy is being transferred to the object irradiated. Bunsen and Roscoe have correlated these factors, and state that identical effects are obtained if the product of the intensity and time is kept constant. This, however, is merely a modification of the Schwartzschild law, which states that intensity multiplied by the time to the exponent K must equal a constant. The factor K is a number slightly less than 1, whereas the Bunsen-Roscoe law is a special case where the exponent is equal to 1, and holds true for a certain limited range of the factors (intensity and time), whereas the Schwartzschild law must be applied for excessive variations in these factors. Therefore, with marked decrease in the intensity the time must be increased more than the proportional decrease in intensity. Accordingly, BACHEM and DUSHKIN (*Proc. Soc. Exp. Biol. and Med.*, 1933, **30**, 700) have experimented to ascertain whether the Schwartzschild or Bunsen-Roscoe law was applicable to the destructive effect of ultraviolet light on bacteria. The method consisted of spreading in a unicellular layer *B. prodigiosus* on an agar plate. By means of a metal shield, the area of exposure to a water-cooled Kromayer lamp can be restricted to a certain field on the plate and at the same time protect the remaining portion. The results of their carefully controlled investigations forced the authors to conclude that the intensity and duration of the exposures were not the only conditions involved, but that some other factor which must be inherent in the bacterial culture itself is also to be considered. To prove this they systematically studied the sensitivity of bacteria to equal amounts of ultraviolet light (keeping time and intensity con-

stant) and found that there was a larger or smaller sensitivity, depending upon the duration between the time of plating and time of exposure, the bacteria being kept at room temperature, 70° F. Their findings compelled the authors to compare short and long exposures of varying intensities, and to base the time comparisons on the validity of either the Bunsen-Roscoe or the Schwartzschild law. Finally, these workers maintain that the Bunsen-Roscoe law is applicable to bacterial destruction by ultraviolet light, but only for those periods in which there is no change in the bacterial sensitivity.

RADIOLOGY

UNDER THE CHARGE OF
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Leprosy.—At Kalihi Hospital, Hawaii, 140 leprous patients were examined with the Roentgen rays by MURDOCK and HUTTER (*Am. J. Roent. and Rad. Ther.*, 1932, **28**, 598). Ages of the patients ranged from 6 to 80 years; 64 per cent were from 16 to 40 years of age. Of the entire group, 108 had roentgenologic signs of osseous disease and 32 were apparently normal. Seventy-two (50 per cent) showed changes in the bones of the hands and feet. Long bones of the arms and legs showed little evidence of disease. Among 75 roentgenograms of the skull, osseous disease was manifest in only 1 instance, and in this case the patient also had syphilis. Fifty cases were chosen and studied because of marked involvement of the soft tissues of the nose and throat, but in no case was there roentgenologic evidence that the nasal bones were affected. In a few cases hyperplasia of one or more ribs was seen. The vertebræ were negative save for a few deformities and arthritides. It was found that the degree of cutaneous leprosy is not a reliable index of bone involvement, and in many cases with large leprous nodules in the skin the bones were not affected. Leprous lesions of bone found in this study were multiform. In many cases the changes were rather minute; in others there was extensive osteitis, osteomyelitis, or cystic degeneration, all in various degrees of dissolution, destruction and regeneration; in a third group destructive or productive arthritis was marked.

Umbrathor in Urography.—RITTER and RATTNER (*Am. J. Roent. and Radium Ther.*, 1932, **28**, 629) have employed umbrathor for roentgenographic examination of the urinary bladder in 3 cases. Umbrathor is a 25 per cent solution of thorium dioxid, a stable brownish liquid, transparent in transmitted light and of milky appearance in reflected light. It is not toxic and is not absorbed by the bladder. When it comes in contact with mucosal surfaces it forms a flocculent coating

thereon and may thus be used to produce relief pictures by inflating the bladder with air after drawing off the excess fluid. In 2 cases a tumor of the bladder was demonstrated and in 1 case the bladder was normal. In a fourth case the authors used the medium to produce a vesiculogram in a case of sterility. The seminal vesicles were well outlined, but the drug remained for several weeks, the umbrathor acting apparently as an obstructing foreign body. It was felt, therefore, that this agent should not be used for vesiculography.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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Auditory Hallucinations in Non-psychotic Children.—LEVIN (*Am. J. Psychiat.*, 1932, **11**, 1119) presents 4 cases of boys who were nonpsychotic and had true auditory hallucinations. Two of them showed what probably are early symptoms of a schizophrenic reaction. The other 2, while maladjusted, showed nothing suggestive of schizophrenia or any other psychosis. All 4 boys were below the average in intelligence, 2 of them conspicuously so. The hallucinatory episodes were studied with regard to the quality of the hallucinatory perception, the localization, the presence of accessory sensations, the content and the apparent functions involved. The hallucinations seem to have participated in the fulfillment of the functions of: (*a*) defense; (*b*) enhancement of self-esteem; (*c*) satisfaction of instinctive cravings and of a desire for pleasure; (*d*) repression of unwelcome instinctive cravings; (*e*) self-punishment in expiation of a sense of guilt. It is emphasized that while certain functions are fulfilled, these probably constitute only one link in the chain of factors which really causes the hallucinations to occur. In 1 case there was evidence of mixed deafness in one ear and in another there was the possibility of some organic auditory disturbance. The significance of the findings for the general problem of projection and their relationship to recent work in eidetics are discussed.

A Combination Therapy of Induced Narcosis and Fever: Its Effect on the "Affective Syndrome."—HACKFIELD (*Arch. Neurol. and Psychiat.*, 1932, **28**, 1169) states that patients suffering from the affective types of psychoses are the most desirable for this form of therapy embodying the artificial induction of fever and a prolonged narcosis. Considering the therapeutic action from the standpoint of the pathogenesis of the affective syndrome: as a result of the many afferent stimuli, conditioned reflexes are established. In the cerebrum, integration of these reflexes takes place according to definite laws. In certain human con-

stitutional types these delicate mechanisms are easily disturbed and a cycle of heterogeneous disorganized reactions follows. Their reflex actions express themselves objectively through the medium of various autonomic functions: salivary secretion or inhibition, emotional states, gastric secretion, etc. Hence, there arises the accompanying autonomic dysfunctions in these psychoses. To affect a recovery, this cycle must be broken, and rest, that is, a reduction in the afferent stimuli, is the best agent. The use of a drug, the therapeutic attack of which breaks this cycle at any point, in either the brain stem or the cerebrum, producing absolute rest, is the goal of this therapy. One is dealing with a physiopathologic process, the psychologic signs and symptoms forming merely a part of the symptom complex, though probably of a psychogenic origin. It is not claimed that after recovery the patient is guarded against further recurrences, but the induced remissions do compare favorably in duration with those obtained with other forms of treatment. However, the apparent specificity of this therapy in the affective syndrome suggests its application in suitable cases, because affective types of psychoses may thus sometimes be terminated within 3 weeks or less which otherwise might be protracted to months or years, or even become chronic.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Hepatic Lesions Associated With Eclampsia and Those Caused by Raising the Intraäbdominal Pressure.—THEOBALD (*J. Pathol. and Bacteriol.*, 1932, **35**, 843) studied the livers of 44 postmortem examinations of women who died from eclampsia. He found the constant feature was not hemorrhage (found in 31, not found in 13), but was degeneration of liver cells almost invariably associated with areas of necrosis. It was into these areas that hemorrhage occurred, when found. Hemorrhages were also observed in some cases in lungs, brain and kidneys. The author conducted a series of experiments on dogs and cats in which he raised the intraäbdominal pressure by injection of normal saline and then using binders studied the lesions produced. These lesions were mainly of the nature of necrosis of liver cells, more apparent in the central areas but sometimes also present in the periphery. The striking feature of these results was the rapidity with which degeneration occurred. The animal which showed the most extensive necrosis was one in which repeated fits were produced of very short duration (½ minute). It is suggested that while hepatic dysfunction renders the human liable to eclampsia, the onset may be determined by the mechanical factors associated with the actual contractions of

labor. It is further suggested that the liver may be damaged by frequent prolonged and violent pains, associated with obstructed labor, and even that a certain amount of damage occurs during a normal labor. He offers the explanation that such damage to liver cells may be an important factor in lowering the resistance of the body to puerperal infection.

A Case Illustrating the Effects of Prolonged Action of Radium.—Ross (*J. Pathol. and Bacteriol.*, 1932, **35**, 899) describes a case of advanced cancer of breast, in which a radium needle (26 originally used in treatment) of strength 2 mg. and covered by a thickness of 0.5 mm. of platinum was accidentally lost in the 4th intercostal space, and which, on Roentgen ray examination, was shown to be in the pericardium. The patient lived for 3 years after this, gradually developing cardiac insufficiency with irregularities and a late jaundice. Postmortem failed to reveal any trace of mammary cancer, but showed a malignant hemangio-endothelioma of the liver with metastases in lungs and bone marrow. The pericardial sac was obliterated by firm adhesions. Near the radioactive focus was found complete necrosis of all tissues, the heart muscle being converted to a structureless hyaline mass. With increasing distance from the needle the necrosis was most severe in the par-arterial areas, while in the perivascular regions the survival of muscle fibers was noted. In further areas were seen hemorrhages and endothelial swelling, beyond which heart muscle was normal; the total zone of necrosis had a radius of 1½ inches. The author ascribes the changes in heart muscle to alterations in its bloodvessels. The spleen and lymphadenoid tissues showed proliferation of macrophages, loss of follicular structure of lymphoid tissue and disappearance of lymphocytes with replacement by plasma cells, and these changes are suggested to have resulted from vascular disturbances due to irradiation. The blood picture showed a relative and absolute lymphopenia. The malignant hemangio-endothelioma in the liver, adjacent to the position of the needle, was thought to be caused by the action of prolonged irradiation on the vessels near the surface of the liver. The author concludes that this case affords additional evidence that the necrotizing and carcinogenic action of gamma radiation results from the susceptibility of the blood vascular system to irradiation.

Normal Fat Content of the Kupffer Cells.—Levine (*Arch. Path.*, 1932, **14**, 345) presents a study of Kupffer cells in 43 presumably normal adults who met sudden death by violence. Four methods of fat staining were employed, namely Sudan III, Nile blue sulphate, Lorrain Smith-Dietrich and Ciaccio. Fat was demonstrated in the Kupffer cells in no less than 41 of the 43 cases; in a few instances there was only a trace, but as a rule there were appreciable quantities. The deposit was always of the character of neutral fat which contained no doubly refracting particles. The lipoid content of the Kupffer cells is roughly parallel to the lipoid content of the liver cells, though the latter commonly contain doubly refracting fat whereas the former do not. No correlation seems to exist between the amount of sudanophil material in the Kupffer cells and the presence of lipoid granules demonstrable by the Lorrain Smith-Dietrich method. The author concludes that neutral fat is normally found in the Kupffer cells.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF
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Significance of Immunity Tests in Epidemiology as Illustrated in Yellow Fever.—Immunity tests are taking an important place in epidemiologic studies of several diseases of man. In diphtheria, scarlet fever and tuberculosis skin tests are commonly used. In poliomyelitis and yellow fever the serum is tested in animals, in the former by a neutralization test and in the latter by a protection test. If a result indicating immunity is obtained by any of these procedures, it is assumed that the person tested has previously been infected with the corresponding causative agent. Such evidence of a preceding immunizing infection is so frequent in persons who give no history of an attack of the disease under investigation that a high prevalence of unrecognized and subclinical cases is commonly assumed. Another possible explanation would be that the immunity tests are not so specific or so reliable as has been believed. HUGHES and SAWYER (*J. Am. Med. Assn.*, 1932, **99**, 978) investigated the specificity and reliability of the yellow fever protection test in mice as an example of the immunity tests used in epidemiologic studies. Serums of persons in Canada and China who could never have been exposed to yellow fever virus were tested for protective power against this virus. In only 1 instance was there any demonstrable non-specific protective power and it was insufficient in amount to give protection with regularity. The test was found to be highly specific and useful as an indicator of past infection.

The Disinfectant Action of Certain Organic Acids.—REID (*Am. J. Hyg.*, 1932, **16**, 540) states that the bactericidal activity of the monobasic series of organic acids, acetic, propionic, butyric and valeric, increases as the series is ascended, that is, with increase in molecular weight and decrease in surface tension. On the other hand, when the inhibitory values of these acids in peptone broth are considered, their activity decreases as the molecular weight decreases. This reversible toxic action of the monobasic series for bacteria, demonstrated when bactericidal and inhibitory action are compared, suggests that surface tension may play a rôle in the disinfection properties of some acids. Replacing an atom of hydrogen, in a normal monobasic acid, with a hydroxyl group, enhances the bactericidal action enormously. The hydroxy-acids of acetic and propionic are approximately 2 to 12 times as bactericidal as the normal acids against B. pyocyaneus, B. typhosus and B. coli. Even against such a resistant organism as S. aureus, they show an increased bactericidal effect. Normal mono-

basic acids, however, exert a greater inhibitory effect on bacteria than their corresponding hydroxy acids. Bactericidal power of the dibasic organic acids, oxalic, malonic and succinic, decreases as the series is ascended. The toxic action of this group against bacteria appears to parallel the degree of dissociation, the more dissociated acids having a greater bactericidal effect. Of the two tribasic acids tested, aconitic was the most toxic for bacteria. This acid was 3 to 36 times more active than citric against B. pyocyaneus, B. typhosus, B. coli and S. aureus. A wide difference exists between the ability of an acid to exert a bactericidal effect and to inhibit growth. Acids which are strongly bactericidal frequently exhibit weak inhibitory powers in liquid media. Oxalic, the most toxic acid in bactericidal dilutions, exhibited a comparatively weak inhibitory effect. Acetic, propionic and butyric acids, which are weakly bactericidal, were the most inhibitory of all the acids tested. Bacillus pyocyaneus is extremely sensitive to disinfection by the organic acids. Not one of these acids exerts a specific effect upon this organism. The hydrogen-ion concentration necessary to inhibit the growth of B. pyocyaneus in peptone broth is not constant, but varies with the kind of acid used. The monobasic acids, the least dissociated of the acids used, inhibit growth at a lower hydrogen-ion concentration than the strongly dissociated acids such as oxalic. It appears that the bactericidal action of the weaker organic acids is not alone dependent upon the cations, but that the undissociated molecules are also active in this respect.

Do Children Who Drink Raw Milk Thrive Better than Children Who Drink Heated Milk?—There is no more vexing question confronting American parents and American health authorities than the following: Shall milk be heated before it is consumed? Most health authorities believe and teach that any milk supply, regardless of how carefully it has been produced, would be made still safer by heating it hot enough and long enough to devitalize any pathogens which might have accidentally found their way into it despite the care taken in producing it. Partly as a result of this teaching there has been a rapid increase in the percentage of milk pasteurized in the United States during the past 30 years. From the beginning of the 20th century to the present time the percentage of milk pasteurized in American cities of 10,000 population and over has increased from a negligible figure to the impressive one of 87.5 per cent. During the past several years, however, raw milk advocates have vigorously contended that heating milk adversely affects its healthfulness and growth-promoting capacity. In support of this claim repeated reference has been made to experiments conducted at Ohio State University and at the British National Institute for Research in Dairying, from which the conclusion is drawn that white rats which are fed upon heated milk will not grow as well as white rats fed upon raw milk. Raw milk advocates have used this material in publicity campaigns in many parts of the United States. They have insisted that these experiments upon white rats justify the conclusion that children will not thrive as well upon heated as upon raw milk. FRANK *et al.* (*U. S. Pub. Health Rep.*, 1932, **47**, 1951) give results of studies of over 3700 children summarized for children of 10 months to 6 years of age: (1) There is no significant difference

between the average weight of children who have received no milk except heated milk and the average weight of children who have received raw milk for more than the latter half of their lives, the respective weights being 33.6 and 33.2 pounds, the insignificant difference being in favor of the children receiving heated milk. (2) The parents of the children receiving predominantly raw milk reported a higher incidence of diphtheria, scarlet fever, intestinal disturbances and rickets than did the parents of the children receiving heated milk only. These workers conclude that the growth-promoting capacity of heated milk plus the supplementary diet received by the average American child of 10 months to 6 years is not measurably less than the growth-promoting capacity of raw milk plus the supplementary diet received by the average American child of 10 months to 6 years.

The Incidence and Time Distribution of Common Colds in Several Groups Kept Under Continuous Observation.—FROST and GOVER (*U. S. Pub. Health Rep.*, 1932, **47**, 1815) present data on the incidence and certain epidemiologic features of the minor respiratory diseases, as indicated by regular semimonthly reports rendered by rather large groups of students at several American universities in widely separated localities and by similar reports from some 1500 families. The students' reports cover 18 months, and the family reports extend through 2½ years. For the year ended May 30, 1925, the mean attack rate in the 10 groups of student reporters was 2947 per 1000, an average of approximately 3 attacks per person. For the entire period, and for each of its major seasonal subdivisions, the attack rates in the several student groups were remarkably uniform, showing no consistent relation to latitude, longitude or climate. In the family group, the attack rates in corresponding periods were consistently lower than in the student groups, but it is possible that this may have been due wholly or in part to more complete reporting by the students. Both in the student and the family groups, the attack rates in corresponding seasons of successive years (1923–1926) showed a declining trend. This may have been due, however, to progressive slackening of interest in reporting. Taking the mean weekly attack rate throughout the year as an axis, the weekly attack rates in each group and in each year were quite consistently below this level from about April 1 to September 1, and generally above this level from September to March, inclusive. The minimum attack rates were observed usually in the latter half of July or the first half of August. During the season of high prevalence, from September to March, inclusive, the incidence curve in each locality exhibited a series of oscillations, constituting a succession of epidemics, each of several weeks' duration, rather irregular in sequence and magnitude, but clearly not attributable to mere chance fluctuation. These epidemics in 6 student groups in widely separated localities showed a striking time correspondence of about the same order as was observed in the influenza epidemics of 1918, 1919 and 1920. Cases reported as influenza constituted about 5.6 per cent of the total reported from the student groups, from December, 1923, to May, 1925, and about 11.7 of those recorded in the family group for the same period of 18 months. While the gross attack rates from all the minor respiratory disorders tended generally to decrease throughout the period of observation, the

reported incidence of so-called influenza tended to increase, being highest in the winter of 1925–1926. The seasonal distribution of cases reported as influenza differed from that of cases classed (clinically) as coryza, in that the latter reached their highest prevalence in the autumn, while the highest incidence of influenza occurred each year in the winter or spring months. Hence, the autumn epidemics observed each year differed from those observed in the late winter and spring in that the latter comprised larger proportions of cases classed as influenza. The increased prevalence of so-called influenza observed in most of the student groups in the winter and spring of 1924–1925 coincided generally with an increase in mortality from influenza pneumonia in the cities represented. However, in individual cities the extent of the increase in mortality bore no obvious relation to that of the increase in prevalence of influenza.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 17, 1933

Influence of Posture Upon the Intraäbdominal Pressure Created by Muscular Effort.—WILLIAM F. MENGERT, and DOUGLAS P. MURPHY (Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania). Measurements of maximum intraäbdominal pressure which can be created by voluntary muscular effort can be made indirectly by recording pressure transmitted to an air-inflated balloon within the vagina. The apparatus, consisting of a rubber balloon and rubber cup, was fixed in the vagina by straps attached to a belt around the waist and readings were made on a mercury manometer.

Initial inflation of the vaginal balloon is of no consequence in recording pressures which can be created, provided the latter are a little more than twice the former. This was proved by testing varying initial inflation pressures both on the human subject and on an apparatus designed to simulate actual conditions as far as possible.

Various factors, of which posture was the most important, influenced the final reading. Eleven hundred and sixty-seven measurements, each representing a maximum straining effort, were made upon 5 healthy, non-pregnant women in seven different postures. The average height to which the mercury column could be raised was 13.7 cm. This represented an actual pressure of 2.65 pounds per square inch.

Among the seven postures, five (lateral prone, recumbent, semi-recumbent, squatting, and standing) were found to vary among themselves in efficiency only insofar as they were influenced by weight of the viscera. Two postures, knee-elbow and sitting, however, were found to have another factor, mechanical advantage of muscular action, in addition to the visceral weight factor.

In sitting, the most efficient posture, the average pressure created was 0.7 pound per square inch better than in lateral prone, the least efficient. Of this difference, only 0.4 pound per square inch could be explained on a visceral weight basis, leaving 0.3 pound per square inch as the greater mechanical effectiveness of the abdominal muscles in this posture.

The Effect of Adrenalin and Sympathetic Stimulation on the Resting Heat Production of the Frog's Sartorius.—Emil Bozler (Eldridge R. Johnson Foundation, University of Pennsylvania). The anaërobic heat production of frog's sartorius was measured using Hill's thermoelectric method. Soaking the muscle in adrenalin 1 to 2,000,000 produces a 30 to 100 per cent increase in anaërobic resting heat production. There is no increase in the tension of the muscle which might account for the increment in heat production. Parallel to this effect there is always an increase in the initial heat and tension produced in a twitch.

Stimulation of the sympathetic trunk also produces an increase in the resting heat production, which may amount to more than 200 per cent of the resting heat production before the stimulation. The effect outlasts the stimulation for about 20 seconds. It is probably of the same nature as that of adrenalin although in these experiments, contrary to Orbeli's, there was no increase in the tension produced.

The Effect of Vagotomy on Muscle Glycogen Resynthesis.—C. N. H. Long and Edith G. Fry (George S. Cox Medical Research Institute, University of Pennsylvania). Debois (*Archiv. Intern. de Pharm. et de Thérap.*, 1931, **41**, 129) has recently claimed that section of the left vagus nerve in the cat prevents the resynthesis of muscle glycogen following its depletion by exercise. Since he has previously claimed that section of this nerve abolishes the formation of muscle glycogen after glucose injection (*Archiv. Intern. de Pharm. et de Thérap.*, 1931, **41**, 65), he concludes: (1) That the secretion of insulin is under the control of the left vagus nerve, and (2) that the resynthesis of muscle glycogen after exercise is also dependent upon the presence of insulin.

These conclusions carry with them implications of great importance. The first of these is that a disturbance of carbohydrate metabolism akin to that found in diabetes mellitus may be produced by an extrapancreatic lesion; second, glycogen formation in muscle under all conditions is an insulin function and the postulates of Meyerhof, that the synthesis observed after exercise occurs from the products of muscular activity alone, are rendered unnecessary.

These questions have been reinvestigated, using the standard white rat fasted for 24 hours as a test animal in preference to the cat. After a 24-hour fast the gastrocnemius muscles of the white rat have a glycogen content that is extremely uniform from animal to animal. In our experience it is invariably 530 ± 50 mgm. per cent.

Both gastrocnemii were uniformly exercised by tetanic stimulation, one removed at once and the other after various intervals of recovery.

The vagotomized rats were studied (*a*) immediately after the vagotomy or (*b*) some 8 to 14 weeks after the operation. The vagotomies were performed either on the right or left side or on both nerves in the

abdomen. In some of the acute experiments both vagi were cut in the neck.

It should be noted at this point that the animals allowed to recover from the various vagotomies grew normally and at death had a normal blood sugar. This is in agreement with the observations of others who used dogs and rabbits.

The rate of resynthesis of muscle glycogen after exercise was entirely unaffected by the various vagotomies, whether they were acute or chronic. The actual figures were: normal rats immediately after exercise, 192 mgm. per cent; 1 hour later, 383 mgm. per cent, an increase of 191 mgm. per cent. Vagotomized rats (average of all experiments) immediately after exercise, 178 mgm. per cent; 1 hour later, 378 mgm. per cent, an increase of 200 mgm. per cent.

This difference in results is not to be explained by the species difference since equally negative findings were obtained on cats. Furthermore, work at present in progress indicates that even pancreatectomy does not abolish muscle glycogen resynthesis after exercise, a finding which is also in sharp distinction from those reported by Debois.

The Blood-shift Due to Muscular Exercise (Staircase-running). —F. S. COTTON (Department of Physiology, University of Sydney, N.S.W., Australia). An attempt to develop a new method for determining the position of the Center of Gravity in man proved successful in that it was shown to possess the advantages of improved accuracy of result and simplicity in execution. The essence of the method is to place the subject (with appropriate precautions for measuring total length) upon a reinforced plank, balanced horizontally, which is spoken of as the balance table so that his Center of Gravity is within some reasonable distance of the fulcrum, and then to measure that distance indirectly by determining the force necessary to completely balance the system. This was accomplished by means of an accurate circular spring balance.

The method, when applied to a considerable number of subjects, gave results showing a distinctly decreased range of individual variation than reported heretofore.

Small changes of Center of Gravity are readily followed, and it is possible to make a reasonably accurate measurement of the to and fro migration of the Center of Gravity due to the movements of respiration, or to any progressive shift of mass in the body. This is accomplished by extending the balance index to constitute a writing lever and to obtain a continuous graphic record of the supporting force, from which the precise position of the Center of Gravity may be readily calculated at any moment. The most convenient procedure, however, is to consider relative changes, and to express them as so many gram centimeters of mass shift in the direction indicated.

These preliminary observations led to the idea of extending previous static investigations so as to make a dynamic study of Center of Gravity. The logical sequence was to systematize the application of the method to different circumstances, and to commence a series of studies in Center of Gravity changes, some of which have been completed and are already published.

The particular investigation which first occupied attention was concerned with an attempt to measure the change of Center of Gravity occurring as a result of muscular exercise, with the object of arriving at some conclusion as to the amount of blood which becomes mobilized in the active muscles, over and above that present in the resting state. The exercise chosen for the investigation was staircase-running, which has the advantage of bringing large muscle masses into action. The method of measuring the mass shift concerned is briefly as follows:

The subject reclines upon the balance table for some 20 or 30 minutes until equilibrium is attained. He then stands up for a period of some 5 minutes, and on reclining again to attain equilibrium, a value of the resulting mass shift is obtained indicating the effect of change of posture only. He then performs the standard staircase exercise, and reclines again until equilibrium is reached once more. The progressive drop of the balance index gives a graphic and quantitative record of the return of blood from the lower limbs in resumption of the resting distribution. Calibration of the record completes the procedure. Several difficulties arose to complicate the investigation, which had to be satisfactorily dealt with before reliable results could be secured. The two chief difficulties were: the advancement of the Center of Gravity due to the slight tilting of the table, and postexercise changes in the length of the subject.

After these difficulties had been overcome and corrections applied the net "mass shift" was determined. Further experiments were carried out in the endeavor to ascertain how much of this "mass shift" could be ascribed to "blood shift." The final value so obtained amounted on an average for some 56 male adults to 30.6 kg. cm. It was argued that if a maximum value can be arrived at for the distance factor of this mass-distance product, a minimal value may be allotted for the quantity of blood in question. Additional experiments were carried out and measurements made, to set a maximal value to this distance factor.

The conclusion was reached that in round figures, as a minimum estimate, *rather less than 500 gm. or rather more than 1 pound of blood is mobilized within the active muscles, in the case of the staircase run, beyond the amount present in the resting recumbent posture.*

The Use of Magnesium Sulphate, Avertin and Sodium Amytal With the Drinker Respirator in the Treatment of Experimental Strychnin Poisoning.—Ben T. Bell and Joseph Stokes, Jr. (Department of Pediatrics and Laboratory of Surgical Research, University of Pennsylvania). These experiments represent an attempt to develop a practicable treatment for extreme convulsive states in children. Strychnin was used as a readily controllable convulsant and cats were used almost exclusively. The object was to discover a narcotic drug capable of controlling convulsions and insuring recovery from more than the ordinary lethal dose of the convulsant. The Drinker respirator was used to permit administration of the narcotic in dosage sufficient to paralyze respiration.

1. Influence of artificial ventilation upon the lethal dose of the anesthetic agent alone.

Magnesium sulphate, avertin, and sodium amytal were tested. Magnesium sulphate, by intramuscular and intraperitoneal injection, killed in the same dosage as in the case of animals not placed in the respirator; with intrathecal injection the lethal dose was very slightly increased by the respirator. Avertin, given subcutaneously, had irregular and uncertain narcotic effects; its lethal dose was increased from 550 to 650 mg. per kilogram by the respirator. Sodium amytal intraperitoneally proved most satisfactory: its effects were constant per unit dose, and its lethal dose was increased from 95 to 150 mg. per kilogram by the respirator.

2. Influence of narcotics and respirator upon the lethal dose of strychnin.

Magnesium sulphate, in dosage sufficient to paralyze respiration, uniformly failed to save animals poisoned with strychnin (1 mg. per kg.).

Avertin in dosage of 600 mg. per kilogram, with the respirator, was no more effective than in dosage of 450 mg. per kilogram without the respirator in saving animals poisoned with strychnin (4 mg. per kg.).

Sodium amytal, in dosage of 125 mg. per kilogram (which produced profound narcosis and complete respiratory paralysis) regularly saved animals given as much as 10 mg. of strychnin per kilogram. A smaller dose of sodium amytal (75 mg. per kg.) without the respirator saved animals poisoned with as much as 6 mg. of strychnin per kilogram.

It is concluded that magnesium does not kill by paralysis of the central nervous system alone, but probably by circulatory depression, so that the respirator does not make possible the safe use of large doses; that avertin is variable in its effects and the larger doses available when the respirator is used do not give added protection against strychnin; that sodium amytal is most promising among the three drugs in combating experimental strychnin poisoning, since with large doses of the narcotic and the respirator it is possible to save animals poisoned with 13 times the ordinary lethal dose of strychnin. This indicates also that the cause of death in strychnin poisoning is probably related to the convulsions, and not to the direct depressant action of strychnin upon the central nervous system.

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